PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLISM

International Consensus Statement

(Guidelines according to scientific evidence)

Under the auspices of the
Cardiovascular Disease Educational and Research Trust
Cyprus Cardiovascular Disease Educational and Research Trust
European Venous Forum
International Surgical Thrombosis Forum
International Union of Angiology and
Union Internationale du Phlebologie.

Original Publication: Nicolaides AN, Fareed J, Kakkar AK, Breddin HK, Goldhaber SZ, Hull R, Kakkar VV, Michiels JJ, Myers K, Samana M, Sasahara A, Kalodiki E. Prevention and treatment of venous thromboembolism. International Consensus Statement (Guidelines according to scientific evidence). Int Angiol 2006; 25:101-161

This booklet is a reproduction of the document already published in "International Angiology" with the following alterations for ease of reading: the tables have been placed at the end of the text and recommendations have been highlighted in bold.

Distributed by CDER Trust
28 Weymouth Street, London W1G 7BZ, UK
e-mail: cdertrust@aol.com

First published in 2006

ISBN: 9963-9276-0-2

CONTENTS

CORRESPONDING FACULTY

C Allegra (Italy)
J Arcelus (Spain)
F Becker (Switzerland)
G Belcaro (Italy)
J Bergan (USA)
SD Berkowitz (USA)
R Bick (USA)
M Boisseau (France)
MA Cairols (Spain)
M Catalano (Italy)
D Christopoulos (Greece)
D Clement (Belgium)
E Diamantopoulos (Greece)
D Duprez (Belgium)
B Eklof (Sweden)
B Fagrell (Sweden)
J Fernandes e Fernandes (Portugal)
C Fisher (Australia)
J Fletcher (Australia)
H Gibbs (Australia)
LJ Greenfield (USA)
JT Hobbs (UK)
D Hoppensteadt (USA)
EA Hussein (Egypt)
O Iqbal (USA)
R Kistner (USA)
N Labropoulos (USA)
M McGrath (Australia)
A Markel (Israel)
H Messmore (USA)
M Nakamura (Japan)
L Norgren (Sweden)
S Novo (Italy)
H Partsch (Austria)
J-B Ricco (France)
N Rich (USA)
JH Scurr (UK)
R Sexana (India)
R Simkin (Argentina)
A Strano (Italy)
M Tsapogas (Greece)
M Vandendriessche (Belgium)
M Veller (South Africa)
L Villavicencio (USA)
R Wahi (USA)

ACKNOWLEDGEMENTS

The foundations for this International Consensus Statement were laid down by the European Consensus Statement on the Prevention of Venous Thromboembolism developed at Windsor (UK) in 1991 with support from the European Commission.[1] The European Consensus Statement was subsequently updated by an international faculty and was forged into "The International Consensus Statement" by extensive evaluation of the literature and debate during the International Union of Angiology (IUA) World Congress in London in April 1995.[2] The latter was updated at the IUA European Congress in Rhodes in May 1999 and was published in "International Angiology" in 2001.[3] Subsequent work by the editorial committee and faculty reconvened at Windsor (UK) in January 2005 and further revisions have ensured that the most recent major advances and the supporting evidence available in 2005 and early part of 2006 have been included.

We are grateful to the following companies for their educational grants towards the meetings of the faculty over the years 1991 to 2005: Abbott Laboratories, Advanced Technology Laboratories, AstraZeneca, Aventis, Behringwerke/Hoechst AG, Boehringer Ingelheim Ltd, Braun, Italfarmaco Spa, Kendall UK, Kendall HealthCare Inc, Knoll AG, Leo Pharmaceutical Products, Lilly Industries Ltd, Novamedix, Novartis, Novo Nordisk Pharmaceutical Ltd, N V Organon, Pentapharm, Pfizer, Pharmacia AB, Porton Products Ltd, Sanofi-Synthelabo, SanofiAventis, Tyco Healthcare, and Wyeth-Ayerst Laboratories.

DISCLAIMER

Due to the evolving field of medicine, new research may, in due course, modify the recommendations presented in this document. At the time of publication, every attempt has been made to ensure that the information provided is up to date and accurate. It is the responsibility of the treating physician to determine best treatment for the patient. The authors, committee members, editors, and publishers cannot be held responsible for any legal issues that may arise from citation of this statement.

EVIDENCE AND GRADES OF RECOMMENDATION

We have used the following consistent method for grades of recommendations in keeping with most other guidelines in this area,[4] and first adopted by our group in 1999.

Grade A recommendations are based on level 1 evidence from randomized controlled trials with consistent results (e.g., in systematic reviews), which are directly applicable to the target population. Single randomized controlled trials have

not been accepted as level 1 even when they were of a high quality and methodologically sound, and have been classified as grade B.[5-7]

Grade B recommendations are based on level 1 evidence from randomized controlled trials with less consistent results, limited power, or other methodological problems, which are directly applicable to the target population. Grade B recommendations are also based on level 1 evidence from randomized controlled trials extrapolated from a different group of patients to the target population.

Grade C recommendations are based on level 2 evidence from well-conducted observational studies with consistent results, directly applicable to the target population.

Recent proposals that a Grade C+ category be used instead of B for extrapolation from randomized trials and that A, B or C recommendations be prefaced by the grade 1 or 2 according to the balance of benefits, risks and costs made by the "Seventh ACCP Conference of Anti-thrombotic and Thrombolytic Therapy: Evidence-based Guidelines"[8] have not been used. Developers of national or local guidelines, which include all stakeholders and all relevant healthcare professionals, the public, patients, and healthcare funders, make such judgements more appropriately.

Only fully published, peer-reviewed papers of directly randomized comparisons for each prophylactic method have been used to determine risk reduction (Tables X-XXI) Non-randomized comparisons of outcome in different trials such as those reported by Colditz et al,[9] Mohr et al,[10] and Imperiale and Speroff [11] have not been included as they are potentially biased.

The relationship between the incidence of asymptomatic and the incidence of symptomatic VTE including PE has been known for some time.[12-14] Reduction in the incidence of asymptomatic DVT has recently been shown to be accompanied by a corresponding reduction for symptomatic DVT.[15,16] Demonstration that asymptomatic below knee DVT is associated with subsequent development of the post-thrombotic syndrome[17] also validates adoption of surrogate endpoints for efficacy evaluation. Thus, evidence is presented for surrogate outcomes such as the incidence of asymptomatic DVT at screening as well as clinical outcomes (symptomatic DVT or PE) depending on availability of data.

This document presents the evidence in a concise format and attempts to indicate not only the magnitute of the effect of different prophylactic regimens but also the quality of the studies. Information on safety (clinically relevant bleeding and other adverse effects) is also provided. When randomized controlled studies are not available, the lack of data is stated and recommendations for the design of appropriate studies are made.

Regulatory bodies in Europe and North America now consider the various LMWHs to be distinct drug products. They require clinical validation for specific indications for each drug and that each LMWH must be dosed according to the

manufacturer's label and recommendations. Therapeutic interchange among these products is not appropriate. The choice of LMWH should reflect the level of clinical evidence and the approval of the regulatory authorities for each indication. This is emphasized throughout the document.

Finally, evidence has been provided for and reference has been made to methods of prevention that are rarely or no longer used or the drug has been withdrawn (dextran, antiplatelet therapy, dihydroergotamine, melagatran/ximelagatran) in order to provide a complete picture to the clinicians and researchers who are new in the field. The reasons for no longer recommending these drugs have been stated.

GLOSSARY

APTC: Antiplatelet trialist's collaboration
COC: Combined oral contraceptives
CVD: Chronic venous disease
CVI: Chronic venous insufficiency
DVT: Deep vein thrombosis
FIT: Foot impulse technology
FUT: Fibrinogen uptake test
GEC: Graduated elastic compression
HIT: Heparin induced thrombocytopenia
HRT: Hormone replacement therapy
IPC: Intermittent pneumatic compression
LDUH: Low dose unfractionated heparin
LMWH: Low molecular weight heparin
PE: Pulmonary embolism
Proximal DVT: DVT in popliteal or more proximal veins
PTS: Post-thrombotic syndrome
RCOG: Royal College of Obstetricians and Gynaecologists
RR: Relative risk
THR: Total hip replacement
TKR: Total knee replacement
UFH: Unfractionated heparin
VTE: Venous thromboembolism
VKA: Vitamin K antagonists
WHO: World Health Organization

THE PROBLEM AND THE NEED FOR PREVENTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are major health problems with potential serious outcomes. Acutely, PE may be fatal. In the long term, pulmonary hypertension can develop from recurrent PE. Often overlooked is post-thrombotic chronic venous insufficiency (CVI) occurring as a result of DVT causing deep venous reflux or obstruction with skin changes and ulceration with adverse impact on quality of life and escalation of health care costs. In North America and Europe, the annual incidence is approximately 160 per 100,000 for DVT, 20 per 100,000 for symptomatic non-fatal PE and 50 per 100,000 for fatal autopsy-detected PE.[18-23] The prevalence of venous ulceration is at least 300 per 100,000 and approximately 25% are due to DVT.[24,25] Estimates of the overall annual costs of CVI vary from 600-900 million € (US$720 million-1 billion) in Western European countries[26,27], representing 1-2% of the total health care budget, to 2.5 billion € (US$3 billion) in the USA.[28]

Virchow's triad of factors that predispose to VTE are venous stasis, alterations in blood constituents, and changes in the endothelium; these are as true today as when postulated in the 19th century. It is often necessary for at least two factors to coexist for VTE to occur. Principal clinical predisposing influences are immobilization, trauma, surgery, infection and the post-partum period.[29] Other predisposing influences are age, obesity, malignancy, previous history of venous thrombosis, varicose veins, dehydration and hormone therapy.[23,30-39] In the background for all of these is predisposition due to thrombophilia.[40] The type of risk factor, whether acute or persistent, determines the type and duration of therapy.

Patients admitted to hospital are particularly at risk for VTE and the problem continues after discharge.[16,41-44] Without prophylaxis, the incidence of DVT is high (Tables I-IV)

Although VTE is an appealing target for maximally effective prophylaxis, this goal has been difficult to achieve. Renewed efforts to educate should maximize utilization, coupled with a system of incentives, warnings, and, where feasible, computerized electronic alerts.[44]

GENERAL AND VASCULAR SURGICAL PATIENTS

THE RISK

Patients who undergo non-orthopedic operative procedures are at risk of developing VTE (Tables I-IV) [9,45-49] The risk is increased by age, obesity, malignancy, prior history of venous thrombosis, varicose veins, and thrombophilic states. It is also affected by the nature and duration of the operation, type of anesthesia, immobility, dehydration and sepsis.[30-34,177,178] Known clinical risk factors allow for classification of patients into high, medium or low risk of developing VTE (Tables VI and VII)

Studies in patients having abdominal or pelvic surgery [41,180,181] demonstrate that the risk continues after discharge from hospital. Further studies are needed before recommendations can be made on the optimal duration of prophylaxis.

Despite the use of intra-operative heparin or other perioperative antithrombotic substances, vascular surgical patients are at moderate risk. The incidence of postoperative asymptomatic DVT is of the order of 18% in patients having abdominal vascular surgery and 15% for those having peripheral vascular reconstruction (Table I). The reported incidence of proximal DVT in patients having abdominal vascular reconstruction is 4-6%.[139,141] The incidence of symptomatic VTE within 90 days of major elective or urgent vascular procedures has been found to be 1.7% to 2.8% in one study.[182] A large prospective European registry of vascular surgical procedures showed that the incidence of clinical DVT was 0.9% following aortic procedures and 0.7% following femoro-distal bypass operations.[183]

The risk of VTE in patients undergoing laparoscopic surgery appears to be low. Three small prospective studies in which no prophylaxis was used showed an incidence of DVT detected by duplex ultrasound or venography in the range of 0-2%.[184,185] Other prospective studies in which some form of prophylaxis was used confirmed the low incidence [186-190] with the exception of one in which 11 of 20 patients developed DVT.[191] Large series from surveys,[192-194] registries, [195-198] a literature review [199] and a population study [182] indicate that the risk for clinical post-operative VTE after laparoscopic procedures is less than 1%. The use of prophylaxis in these studies is not reported in detail, but there appears to be a wide variation from none to LMWH in 80% of patients in some hospitals.

Obesity is an independent risk factor for sudden post-operative fatal PE [200,201]. Bariatric surgery is associated with clinical VTE in 1.2% and with fatal PE in 0.3% of cases.[202]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

In the 1970s, **low dose unfractionated heparin (LDUH)** (5000 IU 8 or 12 hourly subcutaneously) was found to reduce both DVT (Level I evidence) and fatal PE.[203-205] During the late 1980s, two published meta-analyses concerning prophylaxis with LDUH compared with no prophylaxis or placebo[46,47] showed that the incidence of asymptomatic DVT was reduced from 22% to 9% (RR 0.41; 95% CI 0.35 to 0.47) and fatal PE from 0.8% to 0.3% (RR 0.39; 95% CI 0.17 to 0.87). The price was a small increase in bleeding complications from 3.8% to 5.9% (RR 1.56; 95% CI 1.21 to 1.99).

A multicenter study has found that **low molecular weight heparin (LMWH)** not only reduces the incidence of fatal PE but also the overall surgical mortality as compared to controls without prophylaxis.[206] Two small randomized placebo-controlled trials in patients having major oncological abdominal surgery[207] and

emergency abdominal surgery[208] demonstrated the effect of LMWH in reducing asymptomatic DVT.

Sixteen studies have compared LMWH with LDUH,[209-223] and six studies compared different doses of LDUH or LMWH [214,225-229]

Nine meta-analyses and systematic reviews have compared LMWH with LDUH.[230-238] There are some differences between the meta-analyses regarding selection of publications. Four of the meta-analyses reported that there was no difference in total mortality comparing LMWH with LDUH.[231,233-235] Two meta-analyses reported reduced incidence of symptomatic PE with LMWH from 0.70% to 0.31% (RR 0.43; 95% CI 0.33 to 0.54) [231,233] and one showed a decrease of symptomatic VTE.[235] The overall conclusion is that there is no large difference between LMWH and LDUH, but the latter has to be given 2-3 times daily whereas LMWH is administered once daily.

LMWHs have a lower risk of HIT than LDUH.[239,240] High dose LMWH is more effective but is associated with a higher incidence of hemorrhagic complications than LDUH, whereas a low dose of LMWH has a similar efficacy but with less bleeding.[233]

Regulatory bodies in Europe and North America now consider the various LMWHs to be distinct drug products. They require clinical validation for specific indications for each drug. Therapeutic interchange among these products is not appropriate.

In a recent double-blind double-placebo randomized study in 2927 (2048 evaluable) patients having high risk major abdominal surgery, fondaparinux 2.5 mg daily was at least as effective as perioperative LMWH (dalteparin 5000 u daily) in preventing venographically detected DVT without any increase in bleeding.[241]

In the meta-analysis by Clagett and Reisch,[46] **dextran** was also analysed and was found to reduce the incidence of fatal PE (RR 0.22; 95% CI 0.11 to 0.44) although the effect of dextran on DVT was relatively small (RR 0.76; 95% CI 0.64 to 0.91). The preventive effect of dextran on fatal PE has been updated and verified.[242] It appears that fibrin formed in the presence of dextran is not cross-linked so that it is easily lysed by the body's natural fibrinolytic activity.[243,244] However, dextran has inherent risks of fluid overload and anaphylactoid reactions[46] and its routine daily use has been abandoned. Currently, the administration of one peri-operative infusion is considered effective in short-stay surgery and is used by some centres in patients where prophylaxis is considered indicated.

Graduated elastic compression (GEC) stockings reduce the incidence of asymptomatic DVT by approximately 50-60% as shown by several studies (Table VIII) and three systematic reviews,[252-254] but the number of patients studied has been too small to assess the effects on PE.

Intermittent pneumatic compression (IPC) (Table IX) reduces the incidence of asymptomatic DVT by approximately 69% (95% CI 58% to 77%) but the number

of patients studied has been too small to assess the effects on PE.

Aspirin reduces DVT by 30% (Table X) and PE by 50% (Table XI)

Combined modalities. Evidence from randomized controlled studies shows that combinations of prophylactic methods are more effective than using each method singly. These include LDUH with GEC (Tables XII and XIII), LDUH and antiplatelet agents,[170] LDUH and IPC,[246,263] dextran and GEC,[269] GEC and IPC, [270,271] and LDUH and dihydroergotamine which is no longer manufactured or used because of the risk of vasospasm. [272-279] However, the number of studies is relatively small for some combinations and more are needed, particularly in high-risk patients. A randomized study involving 2551 patients undergoing cardiac surgery has demonstrated a reduction in the incidence of PE from 4% in the LDUH group to 1.5% in the group receiving LDUH combined with IPC (RR 0.37 95% CI 0.22 to 0.63).[280]

In the majority of studies, the duration of prophylaxis has been for 5-7 days. However, several studies suggest that the risk continues after discharge from hospital.[41,180,281,282] Extended prophylaxis to one month reduces asymptomatic DVT further by approximately 50-70%.[229,283,284] However, further studies are needed to determine the optimum duration of prophylaxis beyond one week in different groups of patients.

In a review of members of the American Society for Bariatric Surgery, 95% of the surgeons routinely used some form of thromboprophylaxis.[285] In one study, a higher dose of LMWH in combination with GEC and IPC was associated with fewer thrombotic events compared to a lower dose group alone (0.6% vs 5.7%). Bleeding was rare occurring in 2/481 patients.[286]

Recommendations

Low-risk patients are those without risk factors undergoing minor surgery. The data are insufficient to make any recommendations. On the basis of risk/benefit ratio and extrapolation from studies in moderate-risk patients, it is the practice in some countries to use **GEC stockings** in addition to early ambulation and adequate hydration **(Grade C).**

Moderate-risk patients are those over the age of 40 years undergoing major surgery for benign disease. The use of **LDUH** 5000 IU commenced pre-operatively and continued twice or three times daily, or **LMWH** initiated and dosed according to manufacturers recommendations for moderate-risk patients are recommended **(Grade A)**. An alternative method, especially in patients at risk for or with active bleeding, is **IPC with GEC compression used continuously until the patient is ambulant (Grade A).**

High- risk patients are those aged over 60 years with additional risk factors. **LDUH** (5000 IU commenced two hours before operation and continued post-operatively three times a day) **(Grade A)** or **LMWH** initiated and dosed according

to the manufacturer's recommendations are recommended **(Grade A).** Both may be combined with mechanical methods **(GEC or IPC) (Grade B). Fondaparinux** (one study) is a **grade B** recommendation.

These recommendations are extrapolated to patients undergoing vascular or bariatric surgical procedures in the absence of evidence from prospective clinical trials **(Grade C). GEC** is contraindicated in patients with lower limb ischemia (**Grade C).**

Laparoscopic surgery for major prolonged procedures will reduce venous flow in the legs and activate blood coagulation.[186,199] Prophylactic subcutaneous LDUH, LMWH, or IPC with GEC are recommended only in patients with additional risk factors **(Grade C).**

UROLOGIC SURGERY

THE RISK

In the 1970s, the incidence of DVT in the absence of prophylaxis was found to be 32% in patients having retropubic prostatectomy and 9% in patients having transurethral resection (Table I). The incidence of symptomatic VTE is currently in the range of 1-5% and PE is the most common cause of postoperative death.[182,287,288]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

One small randomized study demonstrated that IPC was effective in preventing silent DVT when compared with UFH or no prophylaxis[112] (RR 0.27; 95% CI 0.14 to 0.52). LDUH was effective in reducing asymptomatic DVT in three randomized studies in which the control groups did not have prophylaxis (RR 0.22; 95% CI 0.11 to 0.47). [113,117,289] A large study of 579 patients having radical prostatectomy did not find any difference in the number of pelvic lymphocoeles or blood loss between those receiving LDUH and those not having prophylaxis.[290] LMWH has not been studied by randomized controlled studies and there are no studies for patients having transurethral resection.

Recommendations

IPC with GEC is recommended based on one randomized study and by extrapolation from trials in patients having general surgery **(Grade B). LDUH (Grade A)** giving 5000 IU commenced 2 hours before operation and continued three times a day in the postoperative period is recommended. An alternative is **LMWH** initiated and dosed according to the manufacturer's recommendations by extrapolation from general surgery **(Grade C).**

GYNECOLOGY

THE RISK

Thromboembolic complications after gynecological surgery occur with approximately the same frequency as for general surgery. Patients undergoing major gynecological surgery (e.g. over thirty minutes duration) aged 40 years or over have a significant risk of postoperative VTE (Table I). This risk will increase with additional risk factors such as obesity, previous VTE, malignancy or immobility. However, the incidence appears to be much lower for benign gynecological surgery and vaginal procedures (Table I). PE is a leading cause of death following gynecological cancer surgery[291] and accounts for approximately 20% of perioperative hysterectomy deaths.[292] Risk factors for DVT include those listed for general surgery.[293,294]

An additional risk for VTE is the use of estrogen containing **combined oral contraceptives (COC),**[295] which are used by 18% of women in a UK study.[296] COC increase the risk of VTE.[295] However, the absolute risk is small and represents an increase from 5 to 15-30 per 100,000 women years.[297] The latter is lower than the risk of pregnancy, which is estimated at 100 cases per 100,000 maternities. The risk of postoperative VTE showed an increase from 0.5% to 1% for pill users versus non-users in early studies.[298] The absolute excess risk in COC users has to be balanced against the risk of stopping the pill four to six weeks before surgery which includes unwanted pregnancy, the effects of surgery and anesthesia on a pregnancy, and the risks of subsequent termination. Each case should be assessed in relation to additional risk factors. Before major surgery, COC should be discontinued for at least four weeks and alternative contraception advised. If it is elected not to discontinue COC then the patient should receive prophylaxis as if for at least a moderate-risk patient. Other estrogen-containing preparations should be considered to carry the same risk as COC at least until studies become available. In emergency surgery or when COC have not been discontinued, VTE prophylaxis should be given at least as moderate-risk category. COC do not need to be discontinued before minor surgery without immobilisation. Progestogen-only oral contraceptives need not be discontinued even when immobilisation is expected.[299]

Hormone replacement therapy (HRT) should be included as a risk factor for VTE when assessing patients for elective or emergency surgery.[300] HRT does not need to be stopped routinely prior to surgery provided that appropriate thromboprophylaxis is used such as LDUH or LMWH.[301] Transdermal HRT has less effect on blood coagulation and appears to have a lower VTE risk than oral HRT.[302]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

Low-risk patients: A level I study[250] demonstrated a lower DVT rate with the use of GEC (0 vs 4%; $p < 0.05$). On the basis of this study, the risk-benefit ratio, and extrapolation from data from moderate-risk patients, graduated elastic compression stockings should be used in addition to early ambulation and adequate hydration **(Grade B).**

Moderate-risk patients: Subcutaneous **LDUH** (5000 IU, 12 hourly)[150,152,303; 130] or **LMWH** (initiated and dosed according to the manufacturer's recommendations)[304,305] are effective for preventing DVT.

IPC has been shown to be as effective as LDUH or LMWH for preventing DVT when used continuously for five days[129,257,306] with no bleeding complications.[306] Thus, in patients with a high risk of bleeding, IPC can be used as an alternative to heparin prophylaxis until the patient is ambulatory.

Laparoscopic surgery for major prolonged procedures will reduce venous flow in the legs and activate blood coagulation.[186,199] Prophylactic subcutaneous LDUH, LMWH, or IPC combined with GEC are recommended only in patients with additional risk factors **(Grade C).**

High-risk patients: LMWH [130,210,305,306] initiated and dosed according to the manufacturer's recommendations or **IPC** (throughout hospital stay)[129] are equally effective. Randomized controlled studies in patients having gynecologic oncology surgery have shown no difference in efficacy between LMWH and LDUH given three times a day for thromboprophylaxis against DVT or PE and no difference in the risk of bleeding.[210,307-309] The risk of wound hematomas appears to be reduced by avoiding subcutaneous injection near the wound. LMWH has the advantage of once daily injection and is less likely to cause HIT.

Recommendations

Low-risk patients: They should receive **GEC (Grade B)** in addition to early ambulation and adequate hydration.

Moderate-risk patients: LDUH (5000 IU, 12 hourly), **LMWH** (initiated and dosed according to the manufacturer's recommendations) or **IPC** are **Grade A** recommendations. **LMWH** is the preferred method because it has the advantage of once daily injection and is less likely to cause HIT. **IPC** is the method of choice in patients with a high risk of bleeding.

High-risk patients: LMWH (initiated and dosed according to the manufacturer's recommendations) **(Grade A), LDUH** (5000 IU 8 hourly) (Grade A) or **IPC** (throughout hospital stay) **(Grade B)** are recommended. **LMWH** or **LDUH** combined with **IPC or GEC** stockings provides optimal prophylaxis **(Grade B).**

OBSTETRICS

THE RISK

Pregnancy is a risk factor for VTE with a tenfold increase compared with the risk for non-pregnant women. The time of greatest risk is the puerperium. PE remains the leading direct cause of maternal deaths in the UK.[310] Additional risk factors for VTE in pregnancy and the puerperium include obesity, age over 35 years, thrombophilic states, Caesarean section and surgical procedures during pregnancy and the puerperium.[311] Risk assessment for VTE is recommended for all women in early pregnancy.[310]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

The Cochrane Review of VTE prophylaxis in pregnancy and the puerperium examined 8 trials involving 649 women. It was not possible to assess the effects of interventions because of the limited number of trials and the small sample sizes.[312] Large scale randomized trials of currently used interventions are required.

Table XIV summarises management strategies for various clinical situations.

Women at high risk of VTE including those with previous confirmed VTE should be offered pre-pregnancy counselling to agree to a management plan. The thrombotic risk exists from the beginning of pregnancy.

Women with previous VTE or a strong family history of VTE, particularly where VTE occurs at a young age (<50 years) should be screened for inherited and acquired thrombophilia before pregnancy (Grade C). Ideally, all women should undergo assessment of risk factors for VTE in early pregnancy or before pregnancy. This assessment should be repeated if the woman is admitted to a hospital with complications such as hyperemesis or pre-eclampsia that requires bed rest **(Grade C).**

Systematic reviews and retrospective studies have concluded that **LMWH** is now the treatment of choice in pregnancy compared to UH in view of efficacy and safety[313-317] **(Grade B).** The risks of HIT and osteoporosis during pregnancy are reduced with LMWH as compared with LDUH.[318,319]

The overall risk of recurrence of DVT during pregnancy has been reported as 2.0-3.0%[320] and is higher in those with an underlying thrombophilia or idiopathic thrombosis (6%). A further study reported a recurrence rate per 100 patient-years 10.9% during and 3.7% outside pregnancy.[321] **Thus, women in whom a previous VTE occurred in association with a temporary risk factor that is no longer present and no known thrombophilia or additional risk factors should be offered post-partum thromboprophylaxis with LMWH (Grade C). GEC stockings** during pregnancy should be considered in addition to postpartum prophylaxis **(Grade C).** Women in whom a previous VTE was estrogen-related

(pregnancy or the combined contraceptive pill), or additional risk factors are present such as obesity should be started with thromboprophylaxis with **LMWH as early as possible in pregnancy (Grade C).**

Women with thrombophilias have an increased risk of VTE in pregnancy and the risk varies with the specific thrombophilia. **Women with previous VTE and thrombophilia should be offered thromboprophylaxis with LMWH antenatally and throughout the six weeks postpartum (Grade B).**

Women who are on long-term anticoagulant thromboprophylaxis for VTE and women with anti-thrombin deficiency are at very high risk (30%) during pregnancy. **Those on vitamin K antagonists should be advised to switch to LMWH as soon as pregnancy is confirmed because of the risk of embryopathy from warfarin between the 6th and 12th week of pregnancy. In both situations, LMWH dosage should be similar to that used for the treatment of VTE (Grade B).**

Table XV shows the most recent RCOG guidelines[301] for recommended **LMWH dosage in pregnancy.** Further reports since this guideline was published suggest that a once-daily dosage of tinzaparin provides adequate 24-hour cover[322,323] but more studies are needed concerning its safety and especially the risk of osteoporosis.

Women with a previous VTE and a thrombophilia such as protein C deficiency, Factor V Leiden, Prothrombin 20210A or protein S deficiency who are at moderately increased risk of VTE should receive LMWH (e.g. enoxaparin 40mg daily, dalteparin 5000 units daily or tinzaparin 4500 units daily in women of normal body weight) **from early pregnancy (Grade C).**

Women with no personal history of venous thrombosis but who have a thrombophilic defect identified may require thromboprophylaxis. This will depend on the type of thrombophilia, the family history, and the presence of additional risk factors (e.g. obesity, immobilisation and hyperemesis). All should be offered anticoagulant prophylaxis following delivery. **The risk of thrombosis should be discussed with the patient antenatally and GEC stockings should be considered (Grade C).**

Women with **antiphospholipid antibody syndrome** (lupus anticoagulant or anticardiolipin antibodies) and recurrent miscarriages should receive thromboprophylaxis with **unfractionated heparin and low dose aspirin** (75mg/day) [324,325] from the time of diagnosis of pregnancy **(Grade A).** Although such therapy is aimed at preventing pregnancy loss that is related to placental thrombosis, these women are at risk for VTE and prophylaxis with **LMWH should continue for at least 2 to 5 days after delivery.[301] In women with antiphospholipid syndrome and previous VTE, postpartum prophylaxis should be continued for six weeks (Grade C).**

Delivery and the puerperium:

Management of delivery: Patients on LMWH antenatally and who wish epidural

anesthesia should have heparin prophylaxis discontinued with the onset of labour. An epidural or spinal block is not advised for at least twelve hours after prophylactic LMWH administration and 24 hours after therapeutic doses have been discontinued.[326] LMWH should not be given for at least four hours after the epidural catheter has been inserted or removed and the catheter should not be removed within 10 to 12 hours of the most recent injection.[327] For delivery by elective Caesarean section, the woman should receive a thromboprophylactic dose of LMWH on the day before delivery. On the day of delivery the thromboprophylactic dose of LMWH should be given three hours postoperatively or four hours after removal of the epidural catheter (Grade C).

Management of the puerperium: In addition to previous VTE and thrombophilias, other risk factors should be considered for postpartum prophylaxis: age over 35 years, obesity, Caesarean section (particularly an emergency procedure during labour), gross varicose veins, pre-eclampsia and immobilisation (Grade C).

Postpartum thromboprophylaxis is recommended in women with previous VTE, known thrombophilias and other thrombotic risk factors. The first postpartum daily dose of subcutaneous LMWH (enoxaparin 40mg, dalteparin 5000 units daily or tinzaparin 50 U/g) should be given three to four hours after delivery. Postpartum anticoagulation should be continued for a minimum of six weeks in patients with previous VTE or thrombophilia. In other patients, prophylaxis should continue until discharge from hospital, and the need for prophylaxis should be reviewed if the hospital stay continues beyond five days (Grade B).

If a patient does not wish to continue on self-injections of LMWH, **vitamin K antagonists** can be commenced on the first or second postpartum day. LMWH can be discontinued when the INR has been within the target range of 2.0 - 3.0 for two consecutive days. **GEC** stockings can be added to **LMWH** in high-risk patients and should be used where LMWH is contraindicated. **Where anticoagulants are contraindicated, GEC stockings should be worn for at least six weeks following delivery and can be combined with 75mg of Aspirin daily (Grade C).**

Patients who develop VTE during pregnancy or the puerperium should be referred for hematological screening to determine if they have underlying thrombophilia and counselled about the increased risk of COC pills. Progestogen-only contraception is suitable for these women. They should also be counselled about the need for prophylactic treatment in any future pregnancy.

Breast feeding is not contraindicated with either LMWH, unfractionated heparin or warfarin (Grade C).[328,329]

ORTHOPEDIC SURGERY AND TRAUMA

(A) ELECTIVE HIP REPLACEMENT

THE RISK

In the absence of prophylaxis, patients undergoing elective major joint replacement and those with hip fracture have a DVT risk of approximately 50% (Table I).[330-332] The frequencies of proximal DVT (Table II) and PE (Tables III and IV) are also high. Symptomatic events range from 2-5%.[333] Studies on clinical DVT and PE indicate a postoperative risk period of approximately 3 months[331,333,334] (Table V). Recent mortality studies have confirmed a reduced survival for 2-3 months following elective total hip replacement (THR) surgery with the highest death rate initially early after operation.[335,336]

There is a high incidence of proximal DVT (18-36%) in patients having THR[64,67,68,70,73,337-340] in contrast to patients having TKR in whom the preponderance of thrombosis is distal.[83-85,341,342]

Modern THR surgery is performed with a continuing reduction in hospital stay (3-6 days) so that patients are discharged while still at risk. Thus, the majority of clinical events appear after hospital discharge, giving a false impression of a decreasing problem.[182,334]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

The majority of studies in elective orthopedic surgery have been carried out on elective THR patients. Prophylactic methods that have been investigated include aspirin, dextran, fixed LDUH, adjusted dose unfractionated heparin, fixed LDUH with dihydroergotamine (no longer manufactured), LMWH, heparinoid, recombinant hirudin, the direct thrombin inhibitor melagatran (withdrawn due to hepatotoxicity) fixed mini-dose and adjusted doses of vitamin K antagonists, GEC stockings, IPC and foot impulse technology (FIT). To determine the risk reduction for each prophylactic method, only randomized studies with systematic screening tests for DVT are used for this analysis (Tables X, XI, XVI-XVIII).

LDUH (5000 IU 8 or 12 hourly) was found to be effective for reducing DVT from 46.8% to 23.3% (RR 0.50; 95% CI 0.43 to 0.58) (meta-analysis of 20 randomized controlled studies - Level I evidence)[47] in patients having elective THR and was the method of choice in the 1980s.

It has since been demonstrated that **LMWH** is superior to unfractionated heparin for elective THR surgery reducing DVT from 21.2% to 13.8% (RR 0.66; 95% CI 0.52 to 0.84) and PE from 4.1% to 1.7% (RR 0.40; 95% CI 0.19 to 0.84)[231,232,234,236,340,359-363](Level I evidence). Thus, **LDUH** is no longer recommended.

As indicated in the section on "General Surgery", regulatory bodies in Europe and North America now consider the various LMWHs to be distinct drug products. They require clinical validation for specific indications for each drug. Therapeutic interchange among these products is not appropriate.

Randomized controlled studies have shown that **recombinant hirudin** is more effective than LDUH [364-366] or LMWH.[365] Of 2079 patients studied, 1587 were included in the primary efficacy analysis. Overall, DVT was reduced with hirudin 15mg twice daily compared with 40mg enoxaparin from 25.5% to 18.45% (p=0.001; RRR 28.0%). The safety profile was the same in both groups.[365]

Several randomized controlled trials have compared **vitamin K antagonists** with LMWH. **LMWH** was found to be more effective [355,356,367,368] or at least as effective[358] in the prevention of asymptomatic DVT. However, this was at the expence of a slight increase in hemorrhagic complications. When LMWH was started before or immediately after surgery, there was a marked reduction of proximal DVT from 3% to 0.8% (RR 0.28; 95% CI 0.10 to 0.74).[369] Symptomatic DVT was also reduced from 4.4% in the warfarin group to 1.5% in the LMWH group (RR 0.32; 95% CI 0.12 to 0.88). A recent meta-analysis of vitamin K antagonists in orthopedic surgery[370] showed a RR of 0.56 (95% CI 0.37 to 0.84) for DVT and 0.23 for PE (95% CI 0.09 to 0.59) compared with placebo. VKA were less effective than LMWH in preventing total DVT (RR 1.51; 95% CI 1.27 to 1.79) and proximal DVT (RR 1.51; 95% CI 1.04 to 2.17) although the risk of wound hematoma was increased from 3.3% in the VKA recipients to 5.3% in LMWH recipients (RR 2.29; 95% CI 1.09 to 7.75).

In a recent clinical trial on THR patients,[371] 1279 patients were randomized on the third postoperative day to LMWH or to warfarin for the subsequent 6 weeks. The primary endpoint was the overall clinical failure rate i.e. symptomatic VTE (radiologically confirmed), major hemorrhage or deaths. The failure rate was 3.7% in the LMWH group and 8.3% in the warfarin group (p=0.01). Major bleeding occurred in 1.4% in the LMWH group and in 5.5% in the warfarin group. It appears that reduced bleeding seen initially after surgery due to the slow onset of action for warfarin is offset by long-term increased bleeding. Furthermore, national drug registries have shown warfarin to be a major cause of readmission and fatal bleeding.[372,373] With these data, and because of the need for monitoring, the small therapeutic window and the risk of drug interactions, some surgeons find it difficult to see an advantage for vitamin K antagonists over LMWH.

In contrast to LMWH, the pentasaccharide **fondaparinux,** is a pure synthetic chemical compound. It is a potent indirect inhibitor of factor Xa and acts by a catalytic effect facilitating antithrombin binding to activated factor X and represents one of many attributes of heparins. The drug is administered by subcutaneous injection once daily. It has been registered internationally for major orthopedic surgery. Two large randomized controlled trials compared fondaparinux to

enoxaparin.[374,375] Reduction of asymptomatic DVT was 26% (RR 0.74 95% CI 0.47 to 0.89) and symptomatic PE was 56% (RR 0.44 95% CI 0.27 to 0.66) with fondaparinux. For the two studies combined, the incidence of major bleeding was 3% in the fondaparinux and 2.1% in the enoxaparin patients ($p > 0.05$). Fondaparinux may accumulate and increase bleeding in patients with impaired renal function.

A meta-analysis in the early 1990s[170] demonstrated that **antiplatelet therapy** in elective hip surgery is only moderately effective for protection against DVT (RR 0.70; 95% CI 0.61 to 0.82) (Table X) but the observed reduction in the risk of PE was substantial (RR 0.49; 95% CI 0.26 to 0.92) (Table XI). However, the recent PEP study [262,376] showed that aspirin is not as valuable as the meta-analysis suggested. Over 13,000 hip fracture patients were randomized to have either aspirin or placebo. The overall death rate was identical in each group. Risk reduction for symptomatic VTE was from 2.5% to 1.6% and this was only one-half of that expected from LMWH and one-third from pentasaccharide. The reduced risk of VTE was matched by an increased risk of blood transfusion, gastro-intestinal bleeding and wound bleeding. In a supplementary group of 4000 elective hip and knee replacement patients, there was an insignificant difference in symptomatic VTE.[376] The relative weak thrombophylactic effect of aspirin therefore carries an alternative complication rate and its use might deprive patients of safer or more effective prophylaxis.

The Cochrane database [254] and an earlier metaanalysis[252] shows that **graduated elastic compression** is effective in reducing DVT in hospitalised patients, but there are few robust studies specific to orthopedic surgery.[69,377] In addition, there are disadvantages to graduated elastic compression in trauma cases in which the limb has to be regularly inspected. Because other methods of prevention are more effective, GEC stockings on their own are not recommended.

Intermittent pneumatic compression is effective in patients having THR [64,68,344] (Table XVI A) reducing DVT from 43.6% in the control groups to 21% in the compression groups (RR 0.48; 95% CI 0.36 to 0.64) (Level I evidence). It offers an alternative for surgeons with concerns or patients with contraindications to chemical prophylaxis. It can also be used as an additional method for those at particularly high risk. In a recent randomized study[378] in 131 patients having THR and TKR, the combination of LMWH plus IPC was more effective than LMWH plus GEC stockings (DVT incidence zero versus 28%).

Recent data demonstrate that **foot impulse technology (FIT) combined with graduated elastic compression** is effective in reducing the incidence of proximal DVT in patients having hip or knee replacement (Table XVII) with reduced bleeding and swelling. Direct comparisons with chemical prophylaxis are sparse; there is probably superiority to UFH[348] and equivalence with LMWH for THR[350,379] but not for TKR. [351]

Mechanical methods are intuitively attractive to orthopedic surgeons because of the lack of risk for bleeding. The small number of randomized studies available sets mechanical methods at a disadvantage compared with the considerable number of large studies of chemical prophylaxis. Mechanical methods are generally cumbersome and need supervision from health personel. Nevertheless, they offer an alternative during the early postoperative period for surgeons with concerns about bleeding or for patients with contraindications to chemical prophylaxis. They may also be used as an additional method for those at particularly high risk[378] although this aspect requires confirmation with further studies

Modern technology has made IPC devices light, silent, more portable and more effective in preventing stasis by sensing venous volume so that the compression period follows immediately after venous refilling. In addition, different sleeve designs and materials have been used to improve patient compliance.[380]

Melagatran is a direct thrombin inhibitor that had been developed for subcutaneous administration and as the prodrug ximelagatran for oral administration. It had been approved for short-term use in orthopedic surgery in some countries. Four randomized controlled studies have compared melagatran/ximelagatran with enoxaparin.[381-384] When melagatran was administered immediately before surgery and on the evening of surgery and then orally twice a day, the incidence of DVT was lower than with enoxaparin that was started the evening before surgery and continued each evening thereafter. In the EXPRESS trial[381] total VTE was reduced from 26.6% to 20.3% (p=0.0003). Fatal bleeding, critical site bleeding and bleeding requiring re-operation did not differ between the two groups. “Excessive” bleeding, i.e. bleeding as subjectively judged by the local investigator was 1.2% with enoxaparin vs 3.1% with melagatran. When the melagatran/ximelagatran regimen was started after operation, the incidence of DVT was lower in the enoxaparin group (METHRO III)[384] and bleeding rates were the same in both groups. In a North American study where both oral ximelagatran 24 mg b.d. and enoxaparin 30 mg b.d. were commenced the day after THR surgery and continued for 7 - 12 days, venographic DVT plus symptomatic VTE was detected in 4.6% of the enoxaparin group and 7.9% of the ximelagatran recipients (p = 0.03). Major bleeding was less than 1% in both groups.

The melagatran/ximelagatran regimen had been approved by 18 countries across Europe, South America and Asia for short-term prophylaxis in major hip and knee surgery. Because of concerns about an increase in myocardial infarctions, elevation of liver enzymes and a case of fatal liver failure in the long-term studies, the FDA had not given approval. Because of a second case of severe liver damage a week after short-term therapy, melagatran/ximelagatran has been withdrawn from the market and its development terminated (http://www.astrazeneca.com/pressrelease/5217.aspx).

Meta-analysis shows that **spinal and epidural anesthesia** reduce both

thromboembolism and perhaps mortality in hip fractures,[385,386] and TKR.[387-389] This method does not reduce risk sufficiently on its own, but should be regarded as a useful adjunct. Initial European experience suggested that neuraxial anesthesia could be safely used in the presence of LMWH.[390] However, more recently there have been concerns that a spinal hematoma may develop on very rare occasions.[391;392] Guidelines have been suggested.[327,393] LMWH (or pentasaccharide) can be given safely four hours after removal of the epidural catheter (see pregnancy). However, LMWH or pentasaccharide should be avoided whilst a continuous postoperative neuraxial block is in place. The catheter should not be inserted until serum levels of the chemical agent used are at their lowest. This means that postoperative administration of the agent is, generally, safer and more predictable than pre-operative administration when epidural analgesia is needed.

Timing of prophylaxis

VTE prophylaxis involves a balance of risks and benefits. Chemical prophylaxis poses a dilemma: for a given dose the closer it is administrated to surgery, the better the thromboprophylaxis but the greater is the risk of bleeding complications.[355] In Europe, LMWH is given at a lower dose prior to operation, providing an anticoagulant effect to counteract the intra-operative activation of coagulation factors and venous stasis. However, if a given dose of the drug is administered too long before surgery then, intra-operative blood levels would be inadequate for effective prophylaxis, whereas if given too close to surgery then surgical bleeding is a threat. In North America, LMWH is given after surgery at a higher dose and more frequently. This should reduce the risk of surgical bleeding, yet intra-operative thrombogenesis is not prevented and thrombi may have already begun forming. The drug is now expected to be therapeutic as well as prophylactic. Therefore, prophylaxis needs to be given close but not too close to surgery.[369,394]

IPC and FIT sleeves are available in sterile packages that allow their intraoperative use, reducing the risk of bleeding and the time the patient is not under prophylaxis.[346,395,396]

Duration of prophylaxis in elective orthopedic surgery

Studies in patients having THR[174,181,331,334,355,397-401] demonstrate that there is prolonged risk with 45-80% of all symptomatic events occurring after discharge from hospital.[203,331,402,403]

Randomized controlled studies in patients having THR indicate that **prolonged thromboprophylaxis with LMWH** for up to 35 days is safe and effective irrespective of whether in-hospital prophylaxis was with LMWH or warfarin. It decreases the frequency of venographically detected total DVT, proximal DVT and symptomatic VTE after the seventh day by more than 50%.[359,401,404-407] Further studies are needed before recommendations can be made for prophylaxis beyond 35 days. The optimal duration of prophylaxis is unknown. Epidemiological data on

postoperative death rates indicate a much longer duration of risk in subgroups such as emergency patients (e.g. hip fracture) and patients with co-morbidity (e.g. rheumatoid arthritis) in which vascular deaths dominate.[336,408]

One randomized controlled trial compared warfarin prophylaxis (INR 2-3) for nine days with warfarin extended for one month after hospital discharge. VTE occurred in 5.1% of in-hospital prophylaxis patients and 0.5% in those having extended prophylaxis (RR 9.4; 95% CI 1.2 to 73.5).[409] This study was prematurely terminated because of the superiority of prolonged prophylaxis. As indicated above, it has been subsequently demonstrated that extended prophylaxis with warfarin is associated with more hemorrhagic complications than with LMWH.[371]

Recommendations

LMWH initiated and dosed according to the manufacturer's recommendations, **fondaparinux, oral anticoagulant therapy, IPC** or **FIT combined with GEC** are **Grade A** recommendations. The preferred methods are LMWH or fondaparinux for in-hospital prevention. IPC or FIT combined with GEC stockings are an equivalent alternative to LMWH for those surgeons or anesthetists concerned about bleeding either in all or in certain patients. These devices can be used as long as tolerated and then replaced with chemical prophylaxis for the rest of the five-week period of risk. **Recombinant hirudin (Revasc)** is approved for short-term prophylaxis in approximately 20 European countries and can be used in patients with HIT **(Grade A).**

Prophylaxis with LMWH should be initiated either before or after operation depending on the adopted regimen (Grade A). Fondaparinux should be started at least 6 to 8 hours after surgery. Prophylaxis should be continued for 4-6 weeks with LMWH (Grade A) or fondaparinux (Grade C-extrapolation from hip fracture trial).

(B) ELECTIVE KNEE JOINT REPLACEMENT

THE RISK

Data from THR should not be extrapolated to TKR. The incidence of asymptomatic DVT detected by venography is higher in patients having TKR than THR. However, the incidence of above knee DVT is lower than in patients having THR (see section on THR above).

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

IPC is effective in patients having knee replacement (RR 0.27; 95% CI 0.14 to 0.49) (Table XVI B). One small study demonstrated that **IPC** reduced the incidence of asymptomatic DVT from 65% to 6%.[80] A subsequent study found IPC to be more

effective than aspirin.[345] IPC was was found to be less effective than coumadin for preventing venographically detected DVT (32% vs 19%).[410] **FIT** was also effective in two studies [86,342] but showed inferiority when compared to LMWH in two other studies[351,352] (Table XVII).[411]

A randomized controlled study demonstrated that **LMWH** was more effective than placebo. It reduced venographically detected DVT from 65% in the placebo group to 19% in the LMWH group (RR 0.30; 95% CI 0.16 to 0.58).[412] Subsequent studies demonstrated that LMWH was more effective than LDUH (RR 0.75; 95% CI 0.58 to 0.92) [413,414] or warfarin (RR 0.68; 95% CI 0.62 to 0.76) (Table XVIII).

Fondaparinux (2.5 mg sc once daily starting 6 hrs after surgery) was more effective than enoxaparin (30mg sc b.d. starting 12-24 hrs after surgery) in one study.[415] VTE (defined as venographically detected DVT, symptomatic DVT or symptomatic PE) was reduced from 27.8% in the enoxaparin group to 12.5% in the fondaparinux group (RR 0.45; 95% CI 0.32 to 0.62). However, major bleeding was more common with fondaparinux (2.1% vs 0.2 % p = 0.006). This increased rate of bleeding when fondaparinux was given within 6 hrs of surgery was confirmed in a meta-analysis[416] including this study and three other randomized controlled trials comparing fondaparinux with enoxaparin in patients having orthopedic surgery other than TKR.

Subcutaneous **melagatran** followed by oral **ximelagatran** had the same efficacy and safety as LMWH[382,417]. Three randomized control studies compared oral ximelagatran 24 mg b.d. or 36mg b.d. starting the morning after surgery with adjusted dose warfarin (INR range1.8 to 3.0) starting on the evening after surgery.[418-420] The incidence of DVT was the same in both groups for the 24 mg b.d. dose but the overall VTE or death rate was reduced with the 36 mg b.d. dose. There was no difference in hemorrhagic complications between either dose of ximelagatran and warfarin.

The melagatran/ximelagatran regimen had been approved by 18 countries across Europe, South America and Asia for short-term prophylaxis in major hip and knee surgery. Because of concerns about an increase in myocardial infarctions, elevation of liver enzymes and a case of fatal liver failure in the long-term studies, the FDA had not given approval. Because of a second case of severe liver damage a week after short-term therapy melagatran/ximelagatran has been withdrawn from the market and its development terminated (http://www.astrazeneca. com/pressrelease/5217.aspx).

Duration of prophylaxis

The effect of extending prophylaxis using LMWH to 30-42 days beyond hospitalisation on symptomatic DVT in patients having TKR is less (OR 0.74; 95% CI 0.26 to 2.15; p> 0.05) than in patients having THR (OR 0.33; 95% CI 0.19 to 0.56; p< 0.05) as shown by a systematic review.[16]

Recommendations

LMWH (initiated and dosed according to the manufacturer's recommendations) or warfarin (although less effective) are **Grade A** recommendations. **Fondaparinux** is a **Grade B** recommendation (one study). **IPC or FIT plus GEC** stockings are alternative options but more studies are needed **(Grade B).**

(C) HIP FRACTURE SURGERY

THE RISK

Patients having hip fracture surgery have the highest rates of DVT (46-60%)(Tables I, III, IV) [98,421,422] and fatal PE (2.5-7.5%).[338,422,423] The VTE risk period lasts for 2-3 months after hip fracture surgery in spite of common short-term prophylaxis [333,334] and the 90-day risk of overall death is 13%.[424] After hip fracture, the risk is greater than the standardised mortality, the majority dying of vascular events despite the fact that most patients receive some form of short-term prophylaxis.[335,336]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

Because the risks of DVT and PE including fatal PE are high in patients with hip fracture (Tables I, III, IV), prophylaxis should start as soon as possible after diagnosis and should be the same as that recommended for elective hip surgery.

Reduction in asymptomatic DVT has been demonstrated by **IPC** (RR 0.20; 95% CI 0.07 to 0.55) [344] (Table XVI) and **FIT** in combination with **GEC** [353] (RR 0.32; 95% CI 0.32 to 0.67) (Table XVII). In the most recent study[343] the combined endpoint of PE and proximal DVT using duplex ultrasound was reduced from 12% in the group without prophylaxis to 4% in the IPC group. More studies are needed.

A meta-analysis[170] demonstrated that **antiplatelet therapy** in traumatic orthopedic surgery is only slightly effective for protection against DVT (RR 0.86; 95% CI 0.73 to 1.0) (Table X) but the observed reduction in the risk of PE is substantial (RR 0.40; 95% CI 0.22 to 0.71) (Table XI). In the randomized, placebo-controlled trial of patients undergoing surgery for hip fracture (13,356 patients) or for elective hip or knee arthroplasty (4088 patients), aspirin in a dose of 160 mg daily started preoperatively was used as the primary prophylactic agent for 35 days. In the patients with hip fracture, aspirin reduced the incidence of symptomatic DVT by 29% (95% CI 3% to 48%; p=0.03) and PE by 43% (95% CI 18% to 60%; p=0.002). PE or DVT was confirmed in 105 (1.6%) of 6679 patients assigned aspirin compared with 165 (2.5%) of 6677 patients assigned placebo, which represents an absolute reduction of 9 per 1000 and a proportional reduction of 36% (95% CI 19% to 50%; p=0.0003). However, the complication rate (transfusion requirements and bleeding) offset much of the reduction in symptomatic VTE. The death rate was equivalent in the placebo and aspirin groups.[262] Since other methods are more effective, aspirin on its own is not recommended for routine thrombophylaxis.

In the 1970s, **LDUH** had been found to be effective in reducing asymptomatic DVT (RR 0.51; 95% CI 0.42 to 0.62) (Table XVII) and although an overview of trials had not demonstrated a significant reduction in total PE, there was a significant reduction in fatal PE.[47]

LMWH has been assessed against placebo,[70,229] LDUH,[425] danaparoid,[426] high dose (40mg enoxaparin) LMWH[427] and fondaparinux.[428] LMWH has been found to be equally effective as LDUH without increase in hemorrhagic complications.[429]

Three randomized controlled trials have demonstrated that **VKA** are effective in preventing asymptomatic DVT with a 61% RR reduction for DVT and 66% for proximal DVT, compared with no prophylaxis.[98,430,431] The increase in hemorrhagic complications reported varied from zero to 47% without any increased bleeding in the most recent trial.[98]

Fondaparinux given for 11 days was more effective when compared with LMWH in reducing VTE from 19.1 % to 8.3% (RR 0.46; 95% CI 0.32 to 0.59) and proximal DVT from 4.3% to 0.9% (RR 0.22; 95% CI 0.09 to 0.53).[428] There was no difference in major bleeding but minor bleeding was increased from 2.1 % in the enoxaparin group to 4.1 % in the fondaparinux group ($p = 0.02$). In a second study, patients who received fondaparinux for 7 days were randomized to continuation with fondaparinux or placebo for a further 3 weeks.[432] The incidence of venographic DVT was 1.4% in the extended prophylaxis group and 35.0 % in the placebo group (RR 0.04; 95% CI 0.01 to 0.13). Symptomatic VTE was 0.3% and 2.7% respectively (RR 0.11; 95% CI 0.01 to 0.88). There was no difference in hemorrhagic complications.

Delayed admission to hospital or delayed surgery following hip fractures is associated with a high incidence of DVT developing prior to surgery.[433-436] The incidence of pre-operative DVT as shown by venography can be as high as 62% for all DVT and 14% for proximal DVT when the delay is 48 hours or more.[436] Thus, it is strongly recommended that if surgical delay is anticipated, prophylaxis with LDUH or LMWH is commenced as close to the fracture as possible. Prophylaxis should be restarted once post-operative hemostasis has been achieved.

Recommendations

LMWH (initiated and dosed according to the manufacturer's recommendations), **fondaparinux, adjusted dose VKA (INR range 2-3), or LDUH are Grade A** recommendations. **IPC** or **FIT combined with GEC** should be used when there are contraindications for pharmacological prophylaxis **(Grade B). If surgery is likely to be delayed, prophylaxis should be initiated with LMWH or IPC or FIT plus GEC as close to the fracture as possible (Grade C).**

(D) KNEE ARTHROSCOPY

THE RISK

Knee arthroscopy is a very common procedure varying from a simple diagnostic technique to an extensive repair of injured soft tissues. A tourniquet is usually used.

The incidence of DVT in patients undergoing arthroscopic procedures in the absence of prophylaxis as demonstrated by routine venography or duplex ultrasound is approximately 7% for all thrombi and 1.4% for proximal DVT (Table I).[84,163-168,437] The risk is minimal for diagnostic arthroscopy,[165,334] but the risk is increased if the tourniquet is applied for more than one hour or if therapeutic arthroscopy is performed.[163,165]

Symptomatic VTE occurs after arthroscopy without prophylaxis but it is very rare. In a 10-year prospective study, clinical and radiologically confirmed symptomatic DVT occurred in 0.6%.[165,334] One prospective study found symptomatic PE within 5 weeks after surgery in 1/101 patients who had received LMWH for about two days.[438]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

LMWH was effective compared with no prophylaxis in reducing the incidence of ultrasound detected DVT in two blind randomized studies of patients scheduled for arthroscopy, with 239 patients in one[167] and 130 patients in the other. [168] The incidence of DVT was reduced from 8% in the control groups to 1% in the LMWH groups (RR 0.12; 95% CI 0.03 to 0.53). Bleeding complications were not increased.

Thus, although clinical VTE is uncommon and fatalities are rare, the huge number of patients undergoing knee arthroscopy surgery makes VTE complications potentially relatively frequent. There is a clear correlation between age and degree of trauma with VTE.[84] This justifies prophylaxis in patients with additional risk factors along with prolonged tourniquet application or when extensive surgery beyond a simple diagnostic procedure is performed.

Recommendations

Recommendation for simple diagnostic arthroscopy:

Routine prophylaxis is not recommended unless other risk factors are present (Grade C).

Recommendation for arthroscopic surgery (e.g. ligament reconstructions):

LMWH starting before or after surgery **(Grade B)** or **IPC** in the presence of contraindications to LMWH are recommended **(Grade C)** until full ambulation.

(E) ISOLATED BELOW KNEE INJURIES

THE RISK

Patients with below knee injuries and immobilization have a DVT incidence in the range of 10-35% depending on the type and severity of injury (Table I)[144-149] and carry a risk of clinical PE in the range of 0.4-2.1%.[424] The frequency of symptomatic events is unknown.

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

This group is so heterogeneous that studies and recommendations are difficult to devise.

In one study of 253 patients with plaster casts of which the majority had soft tissue injuries, the ultrasonic incidence of DVT at cast removal was reduced from 17% in the control group to 5% in a LMWH group.[146] It was reduced from 4% in the control group to zero in the LMWH group[146] in another study of 339 patients.[147] Considering both studies the RR was 0.21 (95% CI 0.09 to 0.49)

In patients with lower leg fractures, the five week incidence of venographic DVT was reduced from 18% in the control group to 10% in the LMWH group in one study (n=293) [148] and from 13% to 11% in another (n=150). [149] Considering both studies, the effect of LMWH on DVT was not significant ($p > 0.05$) (RR 0.64; 95% CI 0.39 to 1.05). More studies are needed in well-defined groups of patients.

Recommendations

Currently available data based on small studies of a mixture of different types of injury do not allow routine prophylaxis to be recommended for isolated limb trauma. However, a thorough risk assessment and an approach using **LMWH** standardised by an institution yet individualised for each patient is recommended.

(F) MULTIPLE TRAUMA

THE RISK

The incidence of DVT in patients who have sustained major trauma is in excess of 50% [77,78,439-442] (Table I) and PE is the third leading cause of death in those who survive beyond the first day.[77,443-445] The risk is particularly high in patients with spinal cord injury, pelvic fracture and those needing surgery.[77,78,446-448]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

Patients with polytrauma have a particularly high risk for VTE. The tissue factor released by multiple injuries is potentiated by the likely surgical interventions and the subsequent prolonged immobility [446] produces marked venous stasis. Routine

venography has shown a DVT frequency of 58% in these patients.[77]

Well-designed studies in this area are few and thromboprophylaxis has to be assessed according to the risk for bleeding. However, in the absence of intracranial bleeding and when bleeding is under control, **LMWH** (enoxaparin 30mg bid) started within 36 hours of injury has been shown to be more effective than LDUH (5,000 iu b.d.).[439] It reduced the incidence of venographic DVT from 44% in the LDUH to 31% in the LMWH group (RR 0.70; 95% CI 0.51 to 0.97). The superiority of LMWH to LDUH has been confirmed by a subsequent study and a meta-analysis.[441,449] A study compairing nadroparin fixed daily dose versus a weight-adjusted dose did not demonstrate any significant difference (zero vs 3% DVT).[450]

Three randomized controlled trials have tested the efficacy of **IPC.** The first was in patients with pelvic fractures but the study was small and underpowered so that the DVT reduction from 11% in the control group to 6% in the IPC group was not significant ($p > 0.05$).[343] IPC or FIT was compared with enoxaparin 30 mg b.d. in the second with an incidence of DVT of 2% and 1% respectively.[451] In the third, IPC was compared with FIT with an incidence of DVT of 6% and 21% respectively ($p < 0.02$).[452]

Mechanical methods are attractive if chemical prophylaxis is contraindicated. However, more studies are needed to confirm the efficacy of IPC as this would be the method of choice in patients in whom LMWH is contraindicated because of increased or continuing risk of bleeding.

Recommendations

LMWH starting as soon as bleeding risk is acceptable **(Grade A)** or **IPC** in the presence of contraindications to LMWH **(Grade B)** and continued until full ambulation.

(G) ELECTIVE SPINE SURGERY

THE RISK

The incidence of DVT detected by routine venography in the absence of prophylaxis has been found to be 18% (Table I).[154,453] A review of studies on complications in patients having spinal fusion reported a 3.7% incidence for symptomatic DVT and 2.2% for PE.[454]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

Two small randomized controlled studies comparing no prophylaxis with **LDUH** [455] and with enoxaparin[768] demonstrated that prophylaxis reduces the incidence of asymptomatic DVT from 20% and 10% respectively to zero. In a prospective non-

randomized study of 306 patients[769] venographically detected DVT was found in 6% of those having IPC and in 21% of those without prophylaxis.

Recommendations

Mechanical method: IPC (Grade B)

Drug: LMWH (Grade B)

Initiation: before operation for IPC or after operation for LMWH

Duration: during hospitalization (Grade C).

(H) SPINAL CORD INJURY

THE RISK

Spinal Cord injury

In the absence of prophylaxis the incidence of silent DVT is of the order of 35% (Table I). In this group of patients, PE is the third leading cause of death.[456,457] In a series of 1649 patients undergoing rehabilitation, symptomatic DVT occurred in 10% and PE in 3%.[458]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

LDUH and a combination of **LDUH** with **GEC** were compared with no prophylaxis in a randomized controlled study.[108] The incidence of venographic DVT was 47% and 50% in the control and LDUH groups and 7% in the group that received combined prophylaxis. Subsequently, two small randomized controlled studies[439,459] compared **LMWH** with LDUH. Pooled results in 58 patients showed a trend in reducing asymptomatic DVT by 50% ($p > 0.05$) and changing the risk of proximal DVT from 20% to zero ($p = 0.05$ with Yates' correction). When a combination of LDUH with IPC was compared with LMWH in a randomized controlled study,[460] results shown by routine venography were equally poor (63% vs 66%). It appears that patients with spinal cord injury are not only at high risk for VTE but also a highly resistant group to single prophylactic measures. Further studies are needed.

Recommendations

Drug: IPC and GEC in combination with LMWH. (Grade B)

Initiation: IPC and GEC on admission and LMWH when bleeding risk is acceptable (Grade C)

Duration: LMWH and IPC for three months and continuation with GEC indefinitely (Grade C)

(I) BURNS

THE RISK

There is a spectrum from mild to severe risk in burned patients. All ages are represented. Some patients have additional injuries to other organs or co-morbid diseases, requiring a multidisciplinary approach and intensive care. The incidence of DVT using routine screening with duplex scanning in the absence of prophylaxis varies between 6% and 27% (Table I) [160-162,461] Symptomatic VTE occurs in in 2.4% to 7.0% of patients.[160,462,463]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

Faced with the lack of evidence-based data, prophylaxis has to be individually assessed as it is in multiple injured patients. Therefore, recommendations for burned patients are extrapolated from this group of patients.

Recommendations

Drug: LMWH (Grade C)
Initiation: as soon as it is considered safe to do so
Duration: as long as the patient remains at risk (Grade C)

NEUROSURGERY

THE RISK

The incidence of asymptomatic DVT detected by the fibrinogen uptake test (FUT) in the absence of prophylaxis is approximately 22%, with proximal thrombosis found in 5% (Table I). [123-127,464-466] The risk is particularly high (21%-32%) in patients with glioma[467-471] and persists for a year or more.[467]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

IPC reduced the incidence of silent DVT from 19.1% in the no prophylaxis group to 1.5% in the test group in a randomized controlled study.[124] **GEC and IPC combined with GEC** reduced the incidence of silent DVT from 20% in the absence of prophylaxis to 9% in a subsequent randomized controlled study.[126]

Two large randomized controlled studies compared the effect of **adding LMWH** to **GEC.**[472,473] LMWH with GEC was more effective than GEC alone in reducing not only all DVT (RR 0.62; 95% CI 0.46 to 0.84), but also proximal DVT (RR 0.48; 95% CI 0.28 to 0.84). However, meta-analysis of four randomized controlled studies, three of which involved LMWH, demonstrated that while heparin prophylaxis resulted in a 45% relative risk reduction of venous thromboembolic events, there was a 71% relative risk increase of major bleeding.[474] However, this

relative risk corresponds to a low absolute risk for bleeding. Thus, the number needed to treat was 7.7 for VTE and number needed to harm was 102.

Recommendations

Recommendations for prophylaxis in this group would consist of the use of **IPC in all patients with or without graduated elastic compression stockings (grade A).** Addition of **LMWH** is associated with an increase of efficacy **(grade A).** However, the use of, and timing of LMWH administration should be individualized because of increased risk of bleeding.

MEDICAL PATIENTS

THE RISK

Acute medical conditions such as stroke, congestive heart failure, respiratory disease, infections or myocardial infarction are associated with a high risk of VTE (Table I). [475,476] The patients' overall risk is affected by reduced mobility, cancer with or without chemotherapy (see below) or by patient-related risk factors such as prior VTE, advancing age, obesity, and coagulation disorders which can be either inherited or acquired.[477-482]

A high prevalence of DVT (28% to 33%) has been detected in medical intensive care patients in several studies.[122,483,484] In three other large randomized trials, the prevalence of VTE in the control groups (general medical patients) ranged from 4.96% to 14.9%.[158,485,486] In hospitalized medical patients, asymptomatic proximal DVT has been shown to be associated with a higher mortality rate compared to those with isolated calf DVT.[43]

Autopsy studies show that only 25 % of patients dying from PE in general hospitals have had recent surgery. The rest were immobilised patients with medical illnesses.[203] Overall mortality in medical patients admitted to general hospitals is about 10 %, and about one in 10 hospital deaths (1 % of all admissions) is due to PE.[18,203] Fatal PE is the leading cause of sudden death in hospitalized medical patients, and it is estimated that one of 20 hospitalized medical patients may suffer a fatal PE in the absence of appropriate VTE prophylaxis.[23]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

Acutely ill medical patients

Three randomized controlled studies demonstrated that **LDUH** was effective in preventing asymptomatic DVT when compared to no prophylaxis (RR 0.16; 95% CI 0.06 to 0.43).[91,121,155.] However, significant differences in mortality in hospitalized medical patients using LDUH have not been shown.[487,488] Subsequently, three randomized controlled studies demonstrated that **LMWH** was

effective in preventing asymptomatic DVT when compared to no prophylaxis (RR 0.36; 95% CI 0.22 to 0.59).[51,158,485]. In one of these studies,[158] enoxaparin 20 mg daily was ineffective but enoxaparin 40 mg daily was effective. **LMWH** was also effective in reducing clinically important DVT (symptomatic DVT or PE, sudden death and symptomatic proximal DVT) when compared to no prophylaxis (RR 0.56; 95% CI 0.38 to 0.81).[489] There was no increased bleeding in any of the studies.

Four randomized controlled trials have compared one daily dose of LMWH with 12 or 8 hourly LDUH.[490-493] Although none of the studies showed any advantage for LMWH for asymptomatic DVT on its own, a small advantage was apparent when the results were combined (4.24% vs 5.77%) (RR 0.73; 95% CI 0.56 to 0.97). A meta-analysis of eight studies comparing LMWH with LDUH found a 52% lower incidence of major hemorrhage using LMWH (p=0.049).[494]

In a randomized double-blind trial (ARTEMIS)[495] in acutely ill medical patients, **fondaparinux** (single daily dose of 2.5mg) reduced the incidence of VTE (venographic asymptomatic DVT and symptomatic VTE) from 10.5% with placebo to 5.6% ($p < 0.029$) without increase in the bleeding risk; there were no PE in the fondaparinux group compared with five PE in the placebo group all of which were fatal.

Despite striking evidence supporting DVT prophylaxis with LDUH or LMWH, prophylaxis is underutilized in medical patients compared with surgical patients.[44,475,479,496,497]

All hospitalized medical patients should be assessed for risk of VTE and those at moderate (immobilised patients with active disease) or high risk (stroke, age > 70, cardiac failure, shock, history of previous VTE, malignancy or thrombophilia) should receive prophylaxis.[475] Electronic alerts should be considered for hospitals with computerized order entry systems.[44]

Acute myocardial infarction

Traditionally, patients with acute myocardial infarction are among the highest-risk medical patients for VTE. However, in the presence of the currently aggressive antithrombotic and thrombolytic therapies for myocardial infarction, specific prophylactic regimens are not routinely required.

Acute stroke

Acute ischemic stroke

LDUH was effective in reducing asymptomatic DVT when compared with no prophylaxis in one study (RR 0.30; 95% CI 0.22 to 0.41).[54] A **low molecular weight heparinoid** (danaparoid) was also effective (RR 0.14; 95% CI 0.03 to 0.64).[57] **LMWH** was effective in reducing asymptomatic DVT when compared with no prophylaxis in three randomized studies (RR 0.61; 95% CI 0.49 to 0.77).[52,55,56]

A systematic review of 10 LMWH trials found a significant reduction in DVT and PE but this was at the expence of increased bleeding complications.[498] Two

trials have compared danaparoid[499,500] and one LMWH (enoxaparin)[501] with LDUH. A meta-analysis has calculated reduction of asymptomatic DVT from 22% in the LDUH groups to 13% in the danaparoid or enoxaparin groups (RR 0.59; 95% CI 0.43 to 0.82).[502]

Acute hemorrhagic stroke

In patients with acute hemorrhagic stroke, the value of LDUH or LMWH in the prevention of VTE has not been tested by randomized controlled trials. A recent study randomized 133 patients with documented intracerebral hemorrhage to GEC alone or GEC combined with IPC. The incidence of ultrasound detected asymptomatic DVT on day 10 was reduced from 15.9% in the GEC group to 4.7% in the GEC combined with IPC group (RR 0.29; 95% CI 0.08 to 1.00).[271]

Recommendations

All acutely ill medical patients should be routinely assessed for risk of VTE and considered for thrombophylaxis. In particular, patients over the age of 40 with acute medical illness and/or reduced mobility with one of the following morbidities: acute heart failure NYHA class III/IV, respiratory disease (respiratory failure with or without ventilation or exacerbation of respiratory disease), active cancer requiring therapy, acute infective disease including severe infection and sepsis, rheumatic disease, ischemic stroke or acute myocardial infarction should be considered for prophylaxis. Patients with acute medical illness with reduced mobility and one of the following risk factors: history of VTE, malignant disease or age over 75 should also be considered for prophylaxis.

For acutely ill medical patients prophylaxis with **LDUH 5000 IU t.d.s or LMWH (enoxaparin 40 mg once daily or dalteparin 5000 units once daily) are grade A recommendations.**

In patients with suspected or proven hemorrhagic stroke and in those with ischemic stroke in whom the risks of prophylactic anticoagulant therapy are perceived to outweigh the benefits, **GEC combined with IPC** is recommended. This is a **grade B** recommendation based on extrapolation of data from trials in neurosurgical patients,[123,124,126,261] surgical patients [252] and one randomized controlled study in patients with ischemic hemorrhagic stroke.[271]

CRITICAL CARE PATIENTS

THE RISK

The incidence of DVT in patients in the ICU ranges from 25% to 32% (Table I). Most of these patients have several risk factors for VTE [503,504] and approximately 5% develop DVT prior to admission to the ICU.[157,505-507]

These patients pose a special challenge for VTE prophylaxis [483,506,508] because

they often have multisystem disease which renders routine methods of prevention problematic. For example, thrombocytopenia, renal insufficiency, or active bleeding (often gastrointestinal) may preclude the use of pharmacologic prophylaxis. Peripheral arterial disease or limb amputation may render mechanical prophylaxis ineffective or contraindicated. Thus, it is paradoxical that this group of patients may not be able to safely or effectively use some of the standard prophylaxis measures.

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

Two randomized controlled studies have demonstrated that LDUH is effective in reducing asymptomatic DVT (RR 0.37; 95% CI 0.28 to 0.50) [121,509] LMWH was also effective when compared with no prophylaxis (RR 0.55; 95% CI 0.30 to 0.99) [122] A comparison of LMWH to LDUH in a randomized study of 325 patients demonstrated equal efficacy without any difference in bleeding.[510] Although references to abstracts as evidence for recommendations has been avoided throughout the document, most of the evidence available on prophylaxis in crtical care patients as quoted in this paragraph is in abstract form and thus an exception to the rule has been made.

Recommendations

LDUH or LMWH is recommended unless contraindications limit their use **(Grade A).** For patients with contraindications to pharmacological prophylaxis, the use of **GEC stockings with IPC** is an alternative **(Grade C).** In the absence of contraindications, we suggest **combined mechanical plus pharmacologic prophylaxis (Grade C).** For patients with contraindications to prophylaxis, consider surveillance with duplex scanning.

CANCER PATIENTS

THE RISK

Venous thromboembolism (VTE) is an important and potentially fatal complication in cancer patients. In a nested case controlled study, the odds ratio for development of VTE in patients with cancer was 6.5.[511] The risk of thromboembolic disease varies by type of malignancy with VTE rates of 120 per 10,000 patients described for ovarian malignancy, 117 per 10,000 for primary brain malignancy and 110 per 10,000 for pancreatic cancer.[511] The risk for development of VTE in cancer patients undergoing operation is about twice that for patients without cancer.[512-514] Rates of fatal PE range between 1-5%, with rates of asymptomatic deep vein thrombosis (DVT) of about 30-50%.

Ambulant cancer patients receiving chemotherapy or radiotherapy appear to have a therapy-associated increased rate of VTE. The increased risk appears to be

tumour and stage-dependent. In a breast cancer prevention trial where women at high risk for the development of cancer were randomized to placebo or the hormone therapy Tamoxifen, there was an increased risk for DVT from 0.084% per year for those receiving placebo to 0.13% in the Tamoxifen group.[515] Increase in disease burden in breast cancer is associated with an increased risk of therapy-associated thrombosis with rates ranging from 1% in node negative disease to 17% for advanced disseminated malignancy.[478,516-520] Only limited data are available for patients with other tumour types with primary brain malignancy having reported rates of VTE ranging between 8% and 26%.[467,468] Rates for other tumour types are summarised in tables XIX and X.

The Stockholm surgical studies evaluated potential benefits of pre-operative radiotherapy for reduction of local recurrence in patients with rectal cancer undergoing operative intervention. Patients who received radiotherapy had a higher frequency of VTE within three months of therapy and surgery compared with those who did not (7.5% vs 3.5%).[526]

PROPHYLACTIC METHODS AND RECOMMENDATIONS

General considerations

Surgical patients

LDUH reduces the risk of DVT and fatal PE in patients with malignancy having surgery.[46,130,150,205,520]

LMWH is at least as effective as **LDUH**.[210,220,235]

The intensity of perioperative antithrombotic therapy in cancer patients has been assessed. In gynecologic oncology patients, **LDUH** twice a day was ineffective when compared to no prophylaxis,[128] but administration three times a day was effective (RR 0.47; 95% CI 0.22 to 0.98).[130] In a study of 2070 patients, 65% of whom underwent laparotomy for malignant disease, two doses of the LMWH (dalteparin sodium) were assessed. The frequency of VTE was reduced from 14.9% in patients receiving 2500 anti Xa units to 8.5% in patients receiving 5000 units once daily (RR 0.52; 95% CI 0.37 to 0.74) without any significant increase in perioperative bleeding complications. [226]

Continuation of LMWH for four weeks after discharge home reduces the risk of asymptomatic DVT as demonstrated by venography from 13.8% to 5.5% (RR 0.36; 95% CI 0.16 to 0.79).[527]

Medical cancer patients

LMWH is effective for preventing thromboembolic disease associated with acute medical illness (see section on medical patients).

For ambulant cancer patients receiving therapy out of hospital, only one prospective trial has evaluated antithrombotic intervention. This was a study in 311

patients with metastatic breast cancer receiving chemotherapy randomized to **low dose warfarin** (INR between 1.3 and 1.9) or placebo.[528] The frequency of symptomatic VTE was reduced from 4.5% to 0.8% (Fisher's exact test p=0.038) (RR 0.14 95% CI 0.02 to 1.18). The value of routine primary thromboprophylaxis for patients receiving chemotherapy with other tumor types is not yet established.

For bed-ridden hospitalized cancer patients, there are no specific studies that have evaluated potential benefits from thromboprophylaxis. Therefore, data derived from contemporary trials assessing the value of LMWH in the prevention of thromboembolic disease in acutely ill medical patients may be extrapolated to the cancer population.

Patients receiving radiotherapy

Although patients who receive radiotherapy have a higher frequency of VTE within three months of therapy and surgery compared with those who do not (7.5% vs 3.5%),[526] there are no studies on the value of routine thromboprophylaxis in those receiving radiotherapy. Such studies need to be performed.

Prevention of thromboembolic disease with central venous catheters

Historic data suggest that cancer patients with central venous catheters have a high frequency for development of VTE. The use of **LMWH** (Dalteparin sodium 2500 units once daily) has been shown to be effective in reducing venographic thrombosis from 62% to 6% (RR 0.04; 95% CI 0.01 to 0.42) in one study [477] **Warfarin** (1mg per day) has been shown to be effective in reducing all venographic thrombosis from 37% to 9% (RR 0.17; 95% CI 0.05 to 0.59).[529] However, more recent clinical trials evaluating either **low dose warfarin or LMWH** were not able to demonstrate benefit for routine thromboprophylaxis in this indication.[530-533] This may be due to changes in the way that newer generations of catheters are inserted or maintained.

Recommendations

In surgical patients with cancer, **LDUH** (5000 IU 8-hourly commenced prior to operation) or **LMWH** (initiated and dosed according to manufacturer's recommendations) (Grade A) should be used. **For patients at high risk for development of thromboembolic disease in the post-discharge period** (i.e., those with large volume residual malignant disease, previous history of venous thromboembolic disease), **prolonged thromboprophylaxis with enoxaparin 40 mg once daily for up to 4 weeks after operation** should be considered **(Grade B).**

In ambulant non-surgical cancer patients, data are available only for those with advanced breast cancer receiving chemotherapy (see above). In these patients, use of vitamin K antagonists to maintain an INR of between 1.3 and 1.9 may be considered (Grade B).

For cancer patients hospitalized with acute medical illness, thromboprophylaxis should be based on the risk for VTE determined by the acute medical co-morbidity. **LMWH** (initiated and dosed according to manufacturer's recommendations) or **LDUH** should be used (5000 IU 8-hourly) **(Grade A).**

For cancer patients with central venous catheters, routine use of thromboprophylaxis to prevent central venous catheter associated thrombosis is not recommended **(Grade B).**

THROMBOPHILIA

GENERAL CONSIDERATIONS

The pathogenesis of VTE is multifactorial involving environmental, acquired and genetic risk factors. Congenital predisposition to venous thrombosis (thrombophilia) should be investigated in patients with a documented unexplained thrombotic episode or positive family history.[40,534] The frequency of congenital thrombophilia in consecutive patients with confirmed idiopathic thrombosis occurring outside the clinical setting of surgery, trauma, or cancer is approximately 25%. The most common genetic predisposition in patients of European origin is activated protein C (APC) resistance (Factor V Leiden). Others include: antithrombin (AT), protein C (PC) or protein S (PS) deficiencies, hyperhomocysteinemia, prothrombin G20210A gene mutation or combined thrombophilias.[535-546]

Abnormalities in the fibrinolytic system may contribute to increase the risk of VTE but their clinical relevance has not been well established.[547-549] High plasma levels of factors VIII, IX, and XI are independent risk factors but their congenital character has yet to be established.[550-555]

Not all congenital thrombophilias are associated with the same thrombotic risk. The highest incidence is found in combined defects and antithrombin deficiency and the lowest in FactorV Leiden.[556] In the EPCOT (European Prospective Cohort on Thrombophilia) study, [575] asymptomatic carriers of AT, PC, or PS deficiency of FV Leyden, and 1118 controls were included and followed for 5.7 years on average. The incidence of a first event was 0.8% per year in carriers (1.7% and 1.6% in AT deficiency and combined defects respectively, 0.1% for FV Leiden) and 0.1% in controls.[556] The adjusted RR reported by family studies is 43 (95% CI 10.2 to 180) for antithrombin, 31 (95% CI 7.0 to 139) for protein C and 36 (95% CI 7.9 to 160) for protein S deficiency.[557] The risk of thrombosis when homozygous Factor V Leiden or Prothrombin 20210A defects are present is considered to be extremely high, 50-80 fold compared with the normal population. The risk is also very high when heterozygous defects in both mutations are present.[558]

Acquired disorders associated with an increased risk for venous thromboembolism include the antiphospholipid syndrome, myeloproliferative

disorders and acquired APC resistance. It has been suggested that antithrombin and protein C deficiencies may also increase the risk of thrombosis.

A strong association exists between symptomatic VTE and both primary (without systemic lupus erythematosus-SLE) and secondary (with SLE) antiphospholipid syndromes.[559-561] Among patients with SLE, those with lupus anticoagulant have a much greater VTE risk (OR 5.6; 95% CI 3.8 to 8.3) than those without lupus anticoagulant. Similarly, patients with anticardiolipin antibodies have a greater VTE risk (OR 2.2; 95% CI 1.5 to 3.1) than those without anticardiolipin antibodies. Two more recent studies have also confirmed the risk associated with lupus anticoagulant, anticardiolipin or anti-beta2 GP1 antibodies.[562,563]

Polycythemia vera, essential thrombocythemia and chronic myeloid leukemia have all been identified in descending order of magnitude as conferring an increased risk for VTE, particularly thrombosis of hepatic or portal veins.[564]

Acquired deficiencies of antithrombin and protein C are more common than the respective inherited deficiencies but the association with thrombosis is not demonstrated. They are observed in hypercoagulable states associated with disseminated intravascular coagulation (DIC) such as sepsis from potentially any micro-organism, severe acute respiratory syndrome, severe tissue injury, head injury, fat embolism, severe pancreatitis, solid tumors, hematological malignancies, placental abruption, amniotic fluid embolism, giant hemangiomas, large vessel aneurysms, snake bites, severe transfusion reactions, transplant rejection, and HIT.[565]

Patients with VTE in conjunction with a transient predisposing risk factor have a low risk of recurrence. In contrast, patients with unprovoked idiopathic VTE are candidates for recurrence and thus for thrombophilic screening. The risk of recurrent VTE is not or slightly increased for FactorV Leiden, prothrombin gene mutation and anticardiolipin antibodies (RR 1.4), but it is substantially increased for AT, PC and PS deficiencies and LAC (RR 2.5), and even higher for FactorVIII:C.[550,566,567] The risk of recurrent VTE in patients with AT, PC or PS deficiency is higher during the first year, especially when the first episode is "spontaneous".[568] It has been suggested that the combined use of residual DVT on duplex scanning, a quantitative ELISA D Dimer, and thrombophilia screening after one month of discontinuation of anticoagulant treatment for a first idiopathic VTE can be carried out to help predict different risk groups of VTE recurrence.[569-571]

Acquired hematological abnormalities such as lupus anticoagulant[572,573] and anticardiolipin antibodies[574] are associated with predisposition to VTE and have the most adverse outcomes due to a high rate of recurrence, and if anticoagulation is discontinued there is an increased mortality rate.[575]

The role of thrombophilia in the development of DVT in patients having surgery is controversial, at least for those patients who are given appropriate thrombophylaxis. While a few authors have reported data suggesting an increased

risk of postoperative DVT in carriers of thrombophilia,[576] others have failed to find this association.[577] Of interest, Wahlander and her colleagues have recently reported data suggesting that the carrier status of thrombophilia may expose individuals to an increased risk of late postoperative DVT [578]

IMPLICATIONS FOR PROPHYLAXIS

Among asymptomatic patients with congenital thrombophilia, the value of primary prophylaxis is not yet well determined but in the EPCOT study, long-term prophylaxis did not seem beneficial in asymptomatic relatives of symptomatic probands. Patients should be protected during surgery even when they have minor surgery or minor trauma e.g. ankle sprain or in the presence of any medical condition associated with an increased risk of thrombosis (such as pregnancy). After a first thrombotic event, extra prophylactic care is required in men with a deficiency in natural coagulation inhibitors or multible defects and in women with antithrombin deficiency.[579] In patients with acquired thrombophilic abnormalities, the decision regarding prophylaxis should be made on an individual basis (Grade C).

The reader is referred to the International Consensus Statement "Thrombophilia and Venous Thromboembolism" (Guidelines According to Scientific Evidence) recently published where there is a detailed presentation of etiology, laboratory diagnosis, indications for testing, prevention and treatment in surgical, medical and pregnant patients with thrombophilia as well as the prevention and management of recurrent thromboembolism in the presence of thrombophilia[40].

COST-EFFECTIVENESS OF PREVENTION

Several studies have reported on the cost-effectiveness for approaches commonly used to prevent VTE.[580-588] In medium and high-risk patients the cost of screening, diagnosis and treatment of VTE is so high that currently used recommended methods for prophylaxis are cost-effective (i.e., they optimise use of available resources). Data are not available for low-risk patients concerning cost-effectiveness for currently used prophylactic methods.

Regarding LMWHs, although their cost is greater than unfractionated heparin, the overall cost to treat DVT or PE is less because there is no need for pharmacological monitoring apart from platelet counts, a shorter period in the hospital is required and the complication rates are decreased.[512,589]

Patients on long-term anticoagulation who require interruption of therapy for surgery or other invasive interventions may receive "bridging therapy" with LMWH at home which has been shown to be more cost-effective than continuous infusion of UFH in the hospital.[590,591] Because there has been no thromboprophylaxis study in medical patients comparing LMWH, UFH, and no prophylaxis, a decision-tree

model of 10,000 patients was used to analyze the cost-effectiveness of the three options using data from published studies.[592] Results showed an expected mortality that was lowest in the LMWH group, next in the UFH group, and highest in the no prophylaxis group. Corresponding expected costs of prevention, diagnosis and management of VTE were lowest in the no prophylaxis group, next in the LMWH group and highest in the UFH group. LMWH was superior to UFH by being both more effective and less costly in the base-case analysis as well as in sensitivity analyses in which equal efficacy andequal risk of bleeding were assumed.

TREATMENT

METHODS AND RECOMMENDATIONS

Diagnosis

The clinician should maintain clinical vigilance to consider the possibility of DVT or PE which may occur with leg pain or shortness of breath respectively, but may alternatively have subtle, atypical or even no symptoms.

To diagnose or exclude DVT, the key imaging test is venous ultrasonography.[593] For suspected PE, the Wells Scoring System relies upon a weighted point score for 8 clinical variables and may assist in categorizing clinical likelihood into low, moderate, or high probability.[594] The initial blood test for suspected PE should be a D-dimer ELISA.[595] This is a "rule out" test. If normal, PE is extremely unlikely. However, the D-dimer lacks specificity and will be elevated in PE as well as in multiple other illnesses such as myocardial infarction, cancer, sepsis, the postoperative state, during pregnancy and following childbirth. The best diagnostic imaging test for PE is the chest CT scan.[596] Lung scanning has now been relegated to a second-choice imaging test reserved for patients in whom use of contrast agent might be hazardous such as those with renal failure. A 16-slice multidetector-row CT, for example, can image the entire chest with a single breath-hold of less than 10 seconds and can identify the entire range of PE from massive saddle embolism to sub-millimeter subsegmental PE in 6th-order pulmonary arterial branches.

General considerations

The objectives for treatment of acute DVT are to prevent death and disability from PE, pulmonary hypertension and peripheral venous disease. Further aims are to prevent recurrence of VTE and development of the post-thrombotic syndrome due to persistent venous obstruction and/or dysfunction of the venous valves.[597] Acute extension of DVT and progressive swelling of the leg can result in increased compartmental pressure, possibly leading to phlegmasia cerulea dolens, venous gangrene, and limb loss.

Anticoagulants

In patients with DVT, initial therapy with vitamin K antagonists alone is associated with an unacceptable high rate of recurrent VTE. **Initial parenteral heparin and subsequent long-term oral anticoagulation are both necessary [597,598] (Grade A).**

Treatment with intravenous unfractionated heparin, which generally requires hospitalization, is now rarely used. When using UFH for the initial treatment of DVT, rapidly achieving and maintaining an activated partial thromboplastin time (APTT) within the therapeutic range of 1.5 to 2.5 times the control within 24 hours is likely to reduce the rate of recurrent venous thrombosis[599-601] **(Grade A recommendation).**

Findings from randomized clinical trials indicate that **LMWH** given subcutaneously should replace UFH in treating DVT.[602-612] **LMWH** is effective in patients with PE.[514,613,614] Thus, anticoagulation should usually be started with **LMWH (Grade A recommendation).**

LMWHs have a consistent dose response with predictable bioavailability when given subcutaneously. They do not require hematologic monitoring apart from the platelet count. The need for anti Xa monitoring has been reduced by specific labelling of individual regimens in the context of renal insufficiency or obesity (see pharmacopoeia). They may be administered once a day.[605,615-618] These properties have made LMWH the preferred treatment for patients with uncomplicated DVT as outpatients.[512,597,619-626]

Fondaparinux is a new option for treatment of DVT and PE based on two recent trials.[627,628] Fondaparinux is administered once daily. It has not been reported to cause HIT to date.

A randomized double blind trial (THRIVE III) assessed the efficacy of Ximelagatran, administered without coagulation monitoring vs placebo for 18 months after warfarin for secondary prevention was discontinued at 6 months.[629] The resulting cumulative risks of VTE (3.2% vs 12.7% $p<0.0001$) and PE (0.8% vs 5.2% $p<0.0001$) were significantly lower in the Ximelagatran than in the placebo group. Death from any cause over 18 months occurred in 10 and 12 patients respectively ($p=0.7$).

The melagatran/ximelagatran regimen had been approved by 18 countries across Europe, South America and Asia for short-term prophylaxis in major hip and knee surgery. Because of concerns about an increase in myocardial infarctions, elevation of liver enzymes and a case of fatal liver failure in the long-term studies, the FDA had not given approval. Because of a second case of severe liver damage a week after short-term therapy melagatran/ximelagatran has been withdrawn from the market and its development terminated (http://www.astrazeneca.com/pressrelease/5217.aspx).

Vitamin K antagonist treatment should be adjusted to maintain the INR between 2.0 to 3.0 (target INR 2.5) **(Grade A recommendation).** The risk of bleeding in relation to different INR ranges as reported by several studies is shown in table XXI.

An INR greater than 4.0 is associated with an increased frequency of hemorrhagic complications[633-635] Vitamin K antagonists may be started on the first day of heparin therapy, except when patients require thrombolysis, surgery, or have co-morbidities that predispose to major bleeding.[636,637]

Heparin should be administered for at least five days[636,637] and should be discontinued when the patient's INR is stable within the therapeutic range of 2.0 to 3.0.

Vitamin K antagonists generally should be continued for 3-6 months in patients

with a first episode of VTE and no continuing risk factor.[638-640] Those with continuing risk factors may require more prolonged treatment.[597,638] Patients presenting with recurrent DVT should be treated with a more prolonged anticoagulation regimen compared with those having a first episode.[575] The optimal duration of oral anticoagulant therapy depends on the risk of VTE recurrence.[597,641]

Adjusted doses of LMWH may be used as treatment in special conditions such as pregnancy[642] where vitamin K antagonist therapy is contraindicated and in patients with active cancer who are often resistant to vitamin K antagonists.[643]

Recommendations

When calf DVT is diagnosed, it is recommended that patients be treated with **LMWH followed by warfarin for 3 months.**[638,644] Idiopathic calf DVT should be treated for a longer period [597,645] **(Grade A recommendations).**

Immediate mobilisation with elastic compression stockings to be worn for at least two years at an ankle pressure of 30-40 mmHg (class II) leads to a more rapid reduction of pain and swelling and reduces the occurrence of the post-thrombotic syndrome (PTS).[646-650]

Fondaparinux, a pentasaccharide (Xa inhibitor) is as effective and safe as LMWH or unfractionated IV heparin for the initial treatment of DVT **(Grade A recommendations).**[627,628]

LMWH and renal insufficiency

An increased risk of bleeding has not been reported in patients with renal insufficiency receiving prophylactic dosages of LMWH. However, it is advised that for prophylaxis in patients with severe renal insufficiency, prophylactic doses of LMWH should be adjusted down and the patients monitored for bleeding.

In patients with renal insufficiency LMWH in therapeutic doses poses a high risk of major bleeding due to its prolonged half-life. The actual risk of major bleeding has not been assessed in prospective studies. Such studies would have to be done with each LMWH because of different pharmacological properties. Major bleeding in patients with a creatinine greater than 2 mg/dl and a similar number of patients receiving enoxaparin at equal or greater doses for the same indications has been assessed in one retrospective study. Major bleeding occurred in 1 (2%) of 50 patients with normal renal function and 16 (30%) of 53 patients with serum creatinine greater than 2 mg/dl ($p < 0.001$).[651] Accordingly, the manufacturer's label recommends a fifty per cent dose reduction in patients with severe renal impairment.

Although protamine sulphate is efficatious in stopping LMWH induced bleeding in some animal models there are only limited data for humans.

It has been suggested that in patients with severe renal insufficiency the choice of anticoagulant for full anticoagulation therapy should be unfractionated heparin in

most circumstances based upon risk vs benefit when compared with LMWH and the well known efficacy of protamine sulphate in heparinized patients.[652]

THROMBOLYTIC THERAPY

Thrombolysis for PE

Thrombolytic therapy was initially approved for PE in 1977 but the small number and size of clinical trials, lack of effect on overall mortality, and risk of bleeding complications have impeded its adoption. Thrombolysis in patients with massive PE has been shown to decrease mortality in one trial which enrolled only eight patients.[653] Thrombolytic therapy as an adjunct to anticoagulation appears to reduce the rate of recurrent PE and DVT.[654,655] However, this benefit must be weighed against the risk of increased major hemorrhage. Contraindications such as intracranial disease, recent surgery or trauma preclude its use in some patients who should receive heparin. There is approximately a 1.9% risk of intracranial hemorrhage,[656] but careful evaluation of risk factors such as increasing age should minimise the risk.[657]

Rapid and accurate risk stratification includes clinical evaluation,[479] cardiac biomarkers (troponin level)[658] and right ventricular dilatation or hypokinesis on echocardiography[659-661] or chest CT.[596]

Thrombolysis acts as a "medical embolectomy". Studies show that rapid reduction of the hemodynamic insult by dissolving PE reverses right heart dysfunction. In the long term, thrombolysis improves cardiopulmonary reserve, achieves more complete resolution of pulmonary emboli, prevents or attenuates pulmonary hypertension, and improves functional and symptomatic clinical status.[655,662]

The largest trial of thrombolysis versus anticoagulation alone in PE patients with initially normal blood pressure and right ventricular dysfunction is the MAPPET-3 trial.[663] Overall 256 patients were randomized to heparin plus thrombolysis with tissue plasminogen activator 100 mg/2h versus heparin alone. The combined primary endpoint was in-hospital death or clinical deterioration requiring an escalation of treatment. Treatment escalation was required more than twice as frequently in the heparin-plus-placebo group compared with thrombolysis (24.6% vs. 10.2%, p=0.004) (RR 0.34; 95% CI 0.17 to 0.70). Mortality was low in both groups (3.4% in the heparin-plus-thrombolysis group versus 2.2% in the heparin-plus-placebo group, p=0.71). No fatal bleeding or cerebral bleeding occurred in patients receiving heparin plus thrombolysis. Tissue plasminogen activator given in conjunction with heparin improved the clinical course of stable patients with acute submassive PE.

Recommendation

Thrombolysis is indicated in unstable patients with massive PE who have no

absolute contraindications **(Grade B).** Thrombolysis should be considered in hemodynamically stable patients with moderate or severe right ventricular dysfunction because of their increased likelihood of death[664] **(Grade B).** If thrombolysis is contraindicated, then **mechanical catheter based techniques** [665] or **open surgical embolectomy**[666,667] should be considered (Grade C).

Thrombolysis of DVT

Systemic thrombolysis for DVT may reduce the rates of recurrent DVT and the post-thrombotic syndrome. Early randomized trials of systemically administered streptokinase demonstrated that long-term venous valvular function is better preserved than with heparin alone.[668,669] In an overview of data from six trials, systemic thrombolysis was 3.7 times more effective in producing some degree of lysis than was heparin.[670] In a pooled analysis of 13 randomized studies, only 4% of patients treated with heparin had substantial or complete lysis compared with 45% of patients receiving systemic streptokinase.[671] However, prolonged streptokinase infusions are often unsatisfactory because of frequent allergic reactions and a hemorrhagic rate three-fold higher than that for patients managed with heparin anticoagulation alone.[670] In addition, the frequency of satisfactory lysis is not high enough to generate enthusiasm for systemic thrombolysis.

Catheter-directed thrombolysis for DVT

A catheter-directed technique using urokinase (no longer available) for proximal DVT achieved complete lysis in 72% of patients with concomitant abatement of symptoms.[672] Delivery of the thrombolytic agent within a clot achieves a high concentration of the agent that has not been possible with systemic administration. Because of simultaneous exposure of large segments of thrombus to a high concentration of the thrombolytic agent, thrombolysis can be enhanced, the duration of treatment shortened, the total amount of thrombolytic agent administered lessened and the complications associated with the longer systemic thrombolysis reduced. Once thrombi are lysed, underlying lesions such as stenosis can be managed by angioplasty, and stenting should be performed if recoil occurs.[672,673] Successful catheter-directed thrombolysis for iliofemoral DVT is associated with improved quality of life,[674] improved vein patency and improved venous valve function.[675]

.

Recommendations

Catheter-directed thrombolysis should be considered for proximal DVT, especially iliofemoral thrombosis in active patients at low risk of bleeding where the risk of the post-thrombotic syndrome is higher than for a more distal DVT, **(Grade B recommendation).** Systemic thrombolysis should be avoided because it is less effective, and because the longer duration of therapeutic infusion required increases

the risk of hemorrhagic complications. For patients with PE, peripherally administered intravenous thrombolysis is approved and should be used in patients with massive PE[676] and hypotension. A short, high-concentration thrombolytic regimen (tPA 100mg/2h approved by FDA) is recommended in PE patients with or without hemodynamic impairment if echocardiography demonstrates right ventricular dysfunction[677] **(Grade B recommendation).**

SURGICAL THROMBECTOMY

General considerations

Restoring patency to a thrombosed vein and preserving valve function is important for reducing the risk and severity of the post-thrombotic syndrome. Long-term studies demonstrate improved patency of the iliac vein following thrombectomy with anticoagulation alone.[678-682] A randomized trial of iliofemoral venous thrombectomy with a temporary arteriovenous fistula versus anticoagulation has demonstrated improved venous patency and improved clinical and hemodynamic outcome with preserved valve function in patients randomized to thrombectomy plus a temporary arteriovenous fistula compared with anticoagulation.[680-682] Further studies comparing thrombectomy with conventional treatment are needed to determine recurrence and late outcome rates.

Recommendation

Surgical venous thrombectomy should be considered for patients with symptomatic iliofemoral DVT who are not candidates for catheter-directed thrombolysis (Grade C).

CATHETER-BASED MECHANICAL PROCEDURES

Percutaneous mechanical thrombectomy is now being used to dissolve, fragment and aspirate the thrombi and emboli in patients with acute massive DVT and PE.[683] These procedures are best suited for fresh thrombi less than 10-14 days old. Their efficacy in older thromboemboli is less predictable. Data concerning the short and long-term effects of catheter-based mechanical intervention on the vessel wall, venous valve, and pulmonary vasculature are lacking and are required before its role can be clearly defined.[684] This technique needs further short-term and long-term evaluation and eventually randomized controlled trials before any recommendations can be made.

INFERIOR VENA CAVA FILTERS

A filter device should be inserted in the inferior vena cava of patients with proximal DVT when anticoagulation is contraindicated or when adequate anticoagulation fails to prevent PE.[685,686] Additional high-risk patient groups such as those with multiple trauma and pelvic fracture have been treated successfully with reduction in PE. In a study of 400 patients with symptomatic DVT, all of whom were receiving

heparin or LMWH and were randomized to inferior vena cava filter or not, the incidence of PE was reduced at 12 days but not at 1 year.[687] However, in an eight-year follow-up of these patients, those treated with filters had continued protection against PE with no increase in post-thrombotic syndrome.[687] Complications include insertion site thrombosis, filter migration and caval thrombosis. Retrievable filters are now available and are under investigation.[688-692] However, indications for removal have not been established.

Recommendation

IVC filters are indicated in patients with PE or proximal DVT who have contraindications to anticoagulation or who have suffered recurrent PE while receiving adequate therapeutic anticoagulation **(Grade B).** Consider filter placement in patients with major trauma or pelvic fracture **(Grade C).** Indications for insertion and removal of retrievable IVC filters have not yet been established.

RECURRENT IDIOPATHIC VENOUS THROMBOEMBOLISM

General considerations

VTE used to be considered a time-limited illness that could be effectively treated with 6 months of anticoagulation. However, longitudinal studies indicate a surprisingly high rate of recurrence. At 10 years follow-up, the recurrence rate is approximately 30% in separate Italian[693] and American,[694] registries. Risk of recurrence may be higher in the presence of residual venous thrombosis or elevation of D-dimer.[569,571,695] These disturbing findings have led to trials aiming to determine whether anticoagulation should be extended beyond 3-6 months or perhaps even administered indefinitely.

Studies of prolonged (> 3-6 months) anticoagulation have focused on patients at highest risk of recurrence, those with idiopathic DVT and PE. Regardless of the precise definition of idiopathic, almost every contemporary trial has found that prolonged anticoagulation reduces long-term recurrence by about two thirds.[630,639,644,696-698]

A minor controversy has emerged over the optimal intensity of anticoagulation. One approach tested standard intensity warfarin (after completion of the first three months of treatment) with a target INR between 2.0 and 3.0 versus placebo for a further 24 months. The trial enrolled 162 patients with idiopathic VTE, and three of 79 (3.8%) assigned to warfarin had major bleeding compared with none in the placebo group ($p = 0.09$).[630] To minimize bleeding complications, a novel approach tested low intensity warfarin with a target INR between 1.5 and 2.0. This latter approach only required INR testing once every 2 months[699] (Table XXI).

In an open-label randomized trial of time-limited versus prolonged anticoagulation in 227 patients after a second episode of VTE, 116 patients were randomized to vitamin K antagonists (target INR between 2.0 and 2.85) for an

indefinite period.[575] Among the 116 patients receiving standard intensity and indefinite duration anticoagulation, 10 (8.6%) suffered major hemorrhage. Two of the 10 patients died from bleeding; one had a fatal subarrachnoid hemorrhage, and the other had fatal hemorrhagic pancreatitis.

Minor controversy ensued after publication of a trial showing that standard intensity warfarin was more effective and equally safe as low intensity warfarin in preventing recurrent VTE. The Extended Low-Intensity Anticoagulation for Thrombo-Embolism (ELATE) Trial[631] demonstrated a remarkably low major bleeding rate of 1.1 events per 100 patient years with standard anticoagulation (target INR between 2.0 and 3.0). Among patients receiving low intensity anticoagulation in the ELATE study (target INR between 1.5 and 1.9), the major bleeding rate was exactly the same as in the PREVENT Trial[632,699] 0.9 events per 100 person-years.

Recommendation

Consider **indefinite duration of treatment with vitamin K antagonists** in patients with idiopathic VTE **(Grade B).** The optimal intensity of anticoagulation requires further studies.

TREATMENT IN CANCER PATIENTS

General considerations

Cancer patients who develop an episode of thrombosis are at higher risk for subsequent recurrent thrombosis reported to be with a frequency of 27.1 per 100 patient years for those with cancer compared with 9.0 per 100 patient years for those without cancer.[700] In the same study, the bleeding risk for cancer patients receiving oral anticoagulant therapy was 13.3 per 100 patient years and 2.1 per 100 patient years for non-cancer patients. A further study by Prandoni and colleagues following a cohort of 842 patients, 181 of whom had cancer associated thrombosis, demonstrated a 12 month cumulative incidence of recurrent thromboembolic disease of 20.7% for cancer patients compared with 6.8% for those without. Bleeding was also more frequent in cancer patients (12.4%) than in non-cancer patients (4.9%) (Hazart Ratio: 2.2).[701]

Initial treatment of VTE in cancer

There are no specific studies addressing the initial treatment of VTE in cancer patients. However, many trials that compared **UFH** with **LMWH** for initial treatment of DVT included patients with malignant disease. The meta-analyses of these indicate that unfractionated heparin administered intravenously with routine monitoring of the activated partial thromboplastin time or LMWH administered subcutaneously according to body weight without need for monitoring of the dose are equally effective and safe for initial treatment of DVT. Recommendations

generated for non-cancer patients are extrapolated for use in cancer patients with thrombosis.[702-705]

LMWH therapy for initial treatment of DVT offers an opportunity for outpatient management of patients with cancer-associated thromboembolic disease.[512,514,619,706] Initial management of PE in cancer patients has not been specifically addressed. However, trials have evaluated both intravenous unfractionated heparin and subcutaneous LMWH for treatment of PE.[514,613] A single study of 108 patients with PE has evaluated the potential for outpatient use of the LMWH, dalteparin sodium. There were 22% of patients in this study who had cancer[707] and recurrent thrombosis occurred in 5.6% of patients with a major bleeding rate of 2.9%. Thus, cancer patients with PE may receive either unfractionated or LMWH for initial PE treatment unless they are hemodynamically unstable. Outpatient therapy with LMWH is preferred in cancer patients with a potentially shortened duration of life where quality of life is an essential issue.

The safety and efficacy of **inferior vena cava filters** for management of cancer-associated thrombosis have not been evaluated. In general, unless anticoagulant therapy is contra-indicated due to active bleeding, vena cava filters are not recommended in cancer patients. Early benefits are outweighed by longer-term risks for recurrent thrombosis in patients with malignant disease.[708]

Long-term anticoagulation for secondary prevention of VTE

Cancer patients are both at higher risk for development of recurrent thrombosis and for anticoagulant-associated bleeding with the use of vitamin K antagonists. A study that included 676 patients with cancer-associated VTE was sufficiently powered to define long-term treatment outcomes.[643] All patients received 5-7 days of the LMWH dalteparin sodium in a dose of 200 U/Kg and thereafter they continued with either LMWH in the full treatment dose for the remainder of the month followed by 75-80% of the full treatment dose for the remaining five months or Vitamin-K antagonists with a target INR of 2-3 for six months. The trial demonstrated 52% reduction in the frequency of recurrent thromboembolic events in favour of patients receiving six months of the LMWH dalteparin sodium without any significant increase in the risk of bleeding complications. There were 27 of 336 patients randomized to receive dalteparin who developed recurrence over six months compared to 53 of 336 randomized to receive Vitamin-K antagonist (8.8% vs 17.4%) (RR 0.51; 95% CI 0.33 to 0.79).

A number of prospective randomized clinical trials suggested that cancer patients receiving LMWH over a prolonged period had an improved cancer-associated survival.[525,606,607,643,709-711] These data are of considerable interest since LMWH therapy when compared to placebo was not associated with adverse safety (no increase in bleeding), and thus may represent a potential novel adjuvant anticancer therapy. These preliminary data need to be confirmed by further

prospective clinical trials with appropriate design and power to assess cancer outcome before recommendations can be made.

Recommendations

For initial treatment of VTE in cancer patients, we recommend the use of **intravenous unfractionated heparin or subcutaneous LMWH** administered on a body weight adjusted basis according to manufacturers' recommendations **(Grade A).** LMWH administration is preferred as it allows for outpatient management.

For secondary prevention of recurrent VTE, we recommend use of **LMWH** (dalteparin sodium in a dose of 200 units per Kg once daily for one month and then a reduced dose of 75% of the full treatment dose for a further 5 months) **(Grade B).** Thereafter, those with continuing active cancer or receiving active anti-cancer therapy may be considered for continued anticoagulation with LMWH **(Grade C).**

HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia (HIT) is an important adverse effect of heparin. HIT is reported to occur in 1% of medical, 3% of surgical, and 5% of cardiac surgical therapy or orthopedic surgery patients, and has also been diagnosed in other patient populations.[239,712-720] Progression to overt thrombosis leading to amputation or death is the most serious complication occurring in approximately one-third of patients with HIT.[239,713,718,721] Thrombosis can occur anywhere throughout the venous and arterial circulation. Spontaneous bleeding and petechiae have been reported only rarely.

HIT occurs from exposure to unfractionated heparin (UFH) at prophylactic or treatment doses or from exogenous sources (e.g., catheter flush) [239,712-722] Low molecular weight heparin (LMWH) also causes HIT but at a 2 to 3-fold lower frequency than UFH.[723] The frequency of HIT appears to be decreasing due to the lesser use of UFH, and the increased use of LMWH and non-heparin anticoagulants. Preventive measures include the use of LMWH or fondaparinux rather than UFH for post-surgical prophylaxis, use of porcine rather than bovine UFH, and avoiding unnecessary and prolonged exposure to UFH.[239,419,715] In patients being treated or having been recently treated with heparin, HIT should be suspected on the basis of a 30% decrease in platelet count from baseline in the absence of other reasons for thrombocytopenia. The diagnosis can be made if the platelet count decrease is 50% of baseline, assuming no other reasons for thrombocytopenia. HIT patients can present without thrombocytopenia, i.e., the platelet count does not fall to $<100x10^9$/L (e.g., $350x10^9$/L to $175x10^9$/L)[724] An abrupt decrease in platelet count in the absence of other etiologies and unexplained thrombosis are also characteristics of HIT.[239,713,715] Symptoms typically appear 4 to 14 days after exposure to UFH,[725] or 8 to 14 days after exposure to LMWH.[723] Patients who

received heparin within the prior 100 days can have an immediate, rapid-onset HIT when restarting UFH or LMWH.[725] Delayed-onset HIT has been observed with symptoms appearing several days after discontinuation of UFH.[726]

HIT is an immune response in which antibodies are mainly targeted to the complex of heparin and platelet factor 4 (PF4).[727-729] Immune complexes of PF4-heparin and HIT antibodies that are immunoglobulin G (IgG) bind to platelets via FcγII/α receptors (CD 32),[730] inducing platelet activation, aggregation, and generation of platelet microparticles.[727-731] IgA and IgM have also been identified in HIT patients.[732] HIT antibodies provoke leukocyte and endothelial cell activation that augment both the hypercoagulable and inflammatory states.[733-737] This combined cellular activation leads to a burst of thrombin generation. Of all patients at risk of thrombosis, those with HIT are at highest risk (>40%).[713]

Two types of laboratory assays for HIT are available: platelet function tests (serotonin release and platelet aggregation assays) and ELISA tests that detect antibodies to the PF4-heparin complex.[738,739] Each test provides unique and complementary information.[727,740-742] Functional tests are more specific than the ELISA tests as positive ELISA test results are not always associated with clinical HIT.[723,741-744] Appropriate use and knowledgeable interpretation of the test results are important.

Clinical trials have shown the direct thrombin inhibitors (DTIs) argatroban[745,746] (Grade C) and lepirudin[727,728] (Grade C) to be safe and effective for reducing the risk of thrombosis and associated morbidity / mortality in patients with HIT. These drugs do not cross-react with HIT antibodies. Development of antibodies to lepirudin have been observed in approximately 50% of patients after 10 days treatment, including severe anaphylactic reactions with fatal outcomes in cases of re-exposure to lepirudin.[747,748] The heparinoid, danaparoid, has been used to treat HIT patients with success (Grade B)[749,750] but there are reports that danaparoid cross-reacts with some HIT antibodies leading to treatment failures.[751-754] LMWH can cross-react with most HIT antibodies.[755,756]

Recommendations

Early diagnosis and treatment are important to improve clinical outcomes.[718] Diagnosis of HIT is based on a comprehensive interpretation of clinical and laboratory information.[757]

For the first 14 days of treatment, platelet counts should be performed every 2 days in patients treated with LMWH, daily if treated with UFH, and daily if the patient's risk of developing HIT is high (Grade C). For medical and obstetric patients treated with LMWH exclusively and no prior exposure to UFH it is no longer considered necessary to monitor the platelet count.[715] Patients with co-morbidities are at higher risk of poorer clinical outcomes. All clinical settings including e.g. the emergency department need to be aware of a patient's history of HIT and prior UFH/LMWH exposure.

Laboratory testing should be performed when there is a strong suspicion of HIT (see criteria listed above). Laboratory tests are used to confirm a diagnosis of HIT, but negative results do not exclude this diagnosis.[740-742,758] **It is useful to perform a combination of tests and to repeat testing over a period of several days (Grade B)** [741,742] Initial therapeutic decisions should not be dependent upon a positive laboratory test, but should be based upon clinical findings (i.e., thrombocytopenia and/or new thromboembolic events).

UFH and LMWH should be stopped when the diagnosis of HIT is suspected or confirmed (Grade A).[715] It is not sufficient to merely remove the heparin.[721] Due to the strong hypercoagulable state and high risk of thrombosis associated with HIT, it is recommended that all HIT patients be treated with a non-heparin anticoagulant such as **argatroban, lepirudin, or danaparoid (Grade C).**[715] Differences between these drugs need to be considered when making a clinical treatment decision (e.g., patient renal or liver clearance, drug pharmacokinetics, patient risk of bleeding, prior exposure of patient to lepirudin, physician's experience with the drug, drug availability, cross-reactivity of drug to HIT antibodies, etc.).[759,760] **With danaparoid treatment, if daily platelet counts do not show signs of recovery within 3 days, it is mandatory to check for immune cross-reactivity of patient antibodies to danaparoid using a functional platelet assay and discontinue treatment if positive. LMWH is contraindicated in patients with HIT (Grade A).**[715]

For long-term anticoagulation, vitamin K antagonists can be used. To avoid warfarin-induced limb gangrene/skin necrosis in patients with HIT, these should only be administered after rise of platelet counts with substantial recovery to >100,000/µL or to pre-HIT values (Grade C). Starting doses need to be low (5 mg warfarin, 6 mg phenprocoumon), and given with overlapping administration of argatroban, lepirudin, or danaparoid for at least 5 days.[715,761,762] For special populations of patients with HIT requiring anticoagulation, such as pregnant, pediatric and patients undergoing coronary or other vascular procedures, cardiac surgery, or hemodialysis, specific drug and dose issues need to be considered.

KEY QUESTIONS TO BE ANSWERED

The statements and recommendations made in this document are based on a review of the literature using clearly defined levels of evidence. This process has revealed a number of key questions that require to be addressed by future studies. They are summarised in this final section.

Patient populations

The risk of DVT in the various minimally invasive abdominal surgical procedures and advanced laparoscopic surgery needs to be established.

Recurrence rates of DVT in relation to the residual thrombus, increased D-dimer or risk factors following treatment of the first episode needs to be determined.

A database needs to be created to establish the risk of pulmonary hypertension in patients with PE

Studies on the value of "computerised alerts" are needed to improve efficiency in identifying those in need of prophylaxis.

The value of spiral CT evidence of right heart failure as predictor of a high-risk group of patients with PE requiring thrombolysis needs to be determined.

Prophylaxis

Further studies to assess additive effects on the efficacy, cost-effectiveness and safety of LMWH and mechanical methods in high and medium-risk patients for various medical and surgical specialities are needed.

Possible differences in efficacy of mechanical devices of different design need to be determined such as thigh length vs knee length stockings and pneumatic sleeves, and sequential gradient versus uniform pressure sleeves.

The duration of prophylaxis and value of extended out-of-hospital thrombophylaxis in medical patients need to be determined.

A multicentre trial assessing efficacy, cost-effectiveness and safety of thromboprophylaxis in high-risk pregnant patients is required.

The optimum prophylactic therapy in patients having laparoscopic surgery needs to be determined.

There is a need for further studies to assess the efficacy of mechanical methods in medical patients.

Phase four studies (post-marketing surveillance) to address the long term potential harm of prophylatic methods should be encouraged.

The value of routine thromboprophylaxis in those receiving radiotherapy needs to be evaluated.

There is a need for a randomized, double blind, placebo-controlled trial on safety and efficacy of heparin bridging therapy in at-risk patients on chronic VKA needing temporary interruption for an elective procedure or surgery.

Treatment regimens

The efficacy and safety of thrombolytic therapy in patients with PE and right ventricular dysfunction requires confirmation by Grade A randomized trials.

A randomized study comparing catheter directed thrombolysis of proximal DVT with conventional anticoagulation therapy in preventing the post-thrombotic syndrome is required.

The best approach for LMWH use (e.g. dose adjustment or anti Xa monitoring) in pregnancy, obesity and renally impaired patients needs to be determined (Note: there are increasingly clear guidelines for dose adjustment without anti Xa monitoring).

How do we manage bleeding in patients treated with low molecular weight heparins and fondaparinux? Studies should explore the efficacy of protamine sulphate in patients bleeding from LMWH.

The role of long-term low molecular weight heparin versus vitamin K antagonists in the treatment of DVT and prevention of post-thrombotic syndrome should be determined by randomized trials.

The role of long-term use of elastic stockings in preventing recurrent DVT and post-thrombotic syndrome should be determined.

The value of prognostic markers such as D-dimer, C reactive protein and extent of residual clot burden in guiding the duration of long-term oral anticoagulant therapy needs to be determined.

The use of new drugs as an alternative to UFH or LMWH in patients with HIT needs clinical evaluation.

More randomized control trials are needed to determine the complications / harm produced by prophylatic methods.

The improved survival in patients with cancer treated with LMWH needs to be confirmed by further prospective clinical trials with appropriate design and power to assess cancer outcome before recommendations can be made.

Table I

The frequency of DVT in trauma, surgery and medical patients in the absence of prophylaxis (diagnosed by surveillance with objective methods: Phlebography, FUT or DUS). The listed frequency is true for the total groups of patients. The presence of additional risk factors indicated in the text is likely to increase the risk of thromboembolism for individual patients.

Patient groups	Number of studies	Patients n	DVT incidence (weighted mean)	95% CI
Stroke				
Czechanowski & Heinrich 1981[50]		41	23	
Dahan et al, 1986[51]		27	3	
Elias et al, 1990[52]		15	12	
McCarthy et al, 1977[53]		16	12	
McCarthy & Turner 1986[54]		161	117	
Prins et al, 1989[55]		30	15	
Sandset et al, 1990[56]		50	17	
Turpie et al, 1987[57]		25	7	
Warlow et al, 1972[58]		30	18	
Total	8	**395**	**224 (56%)**	**51% to 61%**
Elective Hip Replacement				
Belch et al, 1982[59]		36	20	
Bergqvist et al, 1979[60]		71	45	
Dechavanne et al, 1974[61]		27	13	
Dechavanne et al, 1975[62]		20	8	
Evarts et al, 1971[63]		56	30	
Gallus et al, 1983[64]		47	25	
Hampson et al, 1974[65]		52	28	
Harris et al, 1977[66]		51	23	
Hoek et al, 1992[67]		99	56	
Hull et al, 1990[68]		158	77	
Ishak & Morley, 1981[69]		41	22	
Kalodiki et al, 1996[70]		14	13	
Mannucci et al, 1976[71]		51	22	
Morris et al, 1974[72]		32	16	
Turpie et al, 1986[73]		50	21	
VTCSG, 1975[74]		30	11	
Welin-Berger et al, 1982[75]		16	5	
Total	17	**851**	**435 (51%)**	**48% to 54%**
Multiple Trauma				
Freeark et al, 1967[76]		124	4	
Geerts et al, 1994[77]		349	201	
Kudsk et al, 1989[78]		38	24	
Shackford et al, 1990[79]		25	1	
Total	4	**536**	**270 (50%)**	**46% to 55%**
Total Knee Replacement				
Hull et al, 1979[80]		29	19	
Kim, 1990[81]		244	80	
Leclerc et al, 1996[82]		57	31	
Lynch et al, 1988[83]		75	28	
Stringer et al, 1989[84]		55	31	
Stulberg et al, 1984[85]		49	41	
Wilson et al, 1992[86]		32	22	
Total	7	**541**	**252 (47%)**	**42% to 51%**

Table 1, contd.

Hip Fracture				
Ahlberg et al, 1968[87]		45	16	
Checketts & Bradley, 1974[88]		26	13	
Darke, 1972[89]		66	11	
Galasko et al, 1976[90]		50	23	
Gallus et al, 1973[91]		23	11	
Kakkar et al, 1972[92]		50	20	
Lahnborg, 1980[93]		69	28	
Montrey et al, 1985[94]		81	22	
Morris & Mitchell, 1976[95]		74	50	
Morris & Mitchell, 1977[96]		76	49	
Myhre & Holen, 1969[97]		55	22	
Powers et al, 1989[98]		63	29	
Rogers et al, 1978[99]		37	19	
Svend-Hansen et al, 1981[100]		65	28	
Xabregas et al, 1978[101]		25	12	
Total	**15**	**805**	**353 (44%)**	**40% to 47%**
Spinal Cord Injury				
Bors et al, 1954[102]		99	58	
Brach et al, 1977[103]		10	9	
Rossi et al, 1980[104]		18	13	
Silver, 1974[105]		32	8	
Watson, 1974[106]		234	42	
Φρισβιε & Σασαηαρα, 1981[107]		17	1	
Μεϱλι ετ αλ, 1988[108]		17	8	
Myllynen et al, 1985[109]		9	9	
Yelnik et al, 1991[110]		22	12	
Total	**9**	**458**	**160 (35%)**	**31% to 39%**
Retropubic Prostatectomy				
Becker et al, 1970[111]		187	39	
Coe et al, 1978[112]		8	1	
Hedlund & Blomback, 1981[113]		28	13	
Kutnowski et al, 1977[114]		12	5	
Mayo et al, 1971[115]		41	21	
Nicolaides et al, 1972[116]		21	10	
Vandendris et al, 1980[117]		33	13	
Williams, 1971[118]		5	4	
Total	**8**	**335**	**106 (32%)**	**27% to 37%**
Transurethral Prostatectomy				
Hedlund, 1975[119]		101	10	
Mayo et al, 1971[115]		20	2	
Nicolaides et al, 1972[116]		29	2	
Total	**3**	**150**	**14 (9%)**	**5% to 15%**
Patients in ICU				
Moser et al, 1981 (FUT)[120]		33	4	
Cade, 1982 (FUT)[121]		60	17	
Fraisse et al, 2000 (Venography)[122]		85	24	
Total	**3**	**178**	**45 (25%)**	**19% to 32%**
General Surgery				
Clagett & Reisch, 1988[46]				
Total	**3**	**54**	**1084 (25%)**	**24% to 26%**

Table 1, contd.

Neurosurgery				
Skillman et al, 1978[123]		48	11	
Turpie et al, 1977[124]		63	12	
Turpie et al, 1985[125]		68	12	
Turpie et al, 1989[126]		81	16	
Zelikovski et al, 1981[127]		20	10	
Total	**5**	**280**	**61 (22%)**	**17% to 27%**
Gynaecological surgery				
Malignancy				
Clarke-Pearson et al, 1983[128]		97	12	
Clarke-Pearson et al, 1984[129]		52	17	
Clarke-Pearson et al, 1990[130]		103	19	
Walsh et al, 1974[131]		45	16	
Total	**4**	**297**	**64 (22%)**	**17% to 26%**
Myocardial infarction				
Emerson & Marks, 1977[132]		41	14	
Handley, 1972[133]		24	7	
Nicolaides et al, 1971[134]		51	8	
Warlow et al, 1973[135]		64	11	
Total	**4**	**180**	**0 (22%)**	**16% to 28%**
Abdominal vascular Surgery				
Hartsuck & Greenfield, 1973[136]		26	7	
Angelides et al, 1977[137]		88	18	
Belch et al, 1980[137]		25	6	
Olin et al, 1993[139]		50	9	
Killewich et al, 1997[140]		48	1	
Hollyoak et al, 2001[141]		21	9	
Total	**6**	**258**	**50 (19%)**	**15% to 25%**
Peripheral vascular reconstruction				
Hamer et al, 1972[142]		21	9	
Passman et al, 2000[143]		53	1	
Hollyoak et al, 2001[144]		28	5	
Total	**3**	**102**	**15 (15%)**	**9% to 23%**
Isolated Lower Limb Injuries				
Hjelmstedt & Bergwall, 1968[144]		76	34	
Abelseth et al, 1996[145]		82	18	
Kujath et al, 1993[146]		127	21	
Kock et al, 1995[147]		163	7	
Lassen et al, 2002[148]		159	29	
Jorgensen et al, 2002[149]		77	10	
Total	**6**	**684**	**119 (17%)**	**15% to 20%**
Gynaecological surgery				
Benign disease				
Ballard et al, 1973[150]		55	16	
Bonnar & Walsh, 1972[151]		140	15	
Taberner et al, 1978[152]		48	11	
Walsh et al, 1974[131]		217	21	
Total	**4**	**460**	**63 (14%)**	**11% to 17%**

Table 1, contd.

Elective Spinal Surgery				
West et al, 1992[153]		41	6	
Oda et al, 2000[154]		110	17	
Total	**2**	**151**	**23 (15%)**	**10% to 22%**
General Medical				
Gallus et al, 1973[91]		15	7	
Belch et al, 1981[155]		50	13	
Prescott et al, 1981[156]		45	4	
Cade, 1982[121]		67	7	
Dahan et al, 1986[51]		131	12	
Schonhofer & Kohler, 1998[157]		196	21	
Samama et al, 1999[158]		288	43	
Oger et al, 2002[159]		234	14	
Leizotovicz et al, 2004[485]		1473	73	
Cohen et al, 2006[495]		323	34	
Total	**10**	**2822**	**228 (8.1%)**	**7.1% to 9.1%**
Burns				
Wait et al, 1990[160]		71	14	
Wahl et al, 2002[161]		30	7	
Wibbenmeyer et al, 20031[162]		148	9	
Total	**3**	**249**	**30 (12%)**	**8.6% to 16%**
Geriatric (>65 years)				
Dahan et al, 1986[51]	**1**	**131**	**12 (9%)**	**5% to 15%**
Knee Arthroscopy				
Stringer et al, 1989[84]		48	2	
Demers et al, 1998[163]		184	33	
Williams et al, 1995[164]		85	3	
Jaureguito et al, 1999[165]		239	5	
Delis et al, 2001[166]		102	8	
Wirth et al, 2001[167]		111	5	
Michot et al, 2002[168]		63	10	
Total	**7**	**832**	**66 (8%)**	**6% to 10%**

Note: In Table 1 the subtotals for DVT for Multiple Trauma should be 230 instead of 270 and for Myocardial Infarction 40 instead of 0

Table II

The frequency of proximal DVT in the absence of prophylaxis diagnosed by surveillance with objective methods (fibrinogen uptake test or venography).

Patient groups	Number of Studies	Number of Patients	Incidence of DVT	95% CI
General surgery (Clagett & Reisch, 1988)[46]	16	1206	83 (6.9%)	5.5 to 8.3%
Elective hip replacement (Imperiale & Speroff, 1994)[11]	25	1436	330* (23%)	20.8 to 25.2%
Total knee replacement (Hull et al, 1979[80] Kim, 1990[81] Leclerc et al, 1996[82] Mckenna et al, 1976[169] Stringer et al, 1989[84] Stulberg et al, 1984[85] Wilson et al, 1991[86]	7	536	41 (7.6%)	5.5 to 10.1%

* This number is an estimate from the percentage given in the paper.

Table III

The frequency of clinical pulmonary embolism* in the absence of prophylaxis.

Patient groups	Number of Studies	Number of Patients	Clinical PE	95% CI
General surgery (Clagett & Reisch, 1988)[46]	32	5091	82(1.6%)	1.3 to 2.0%
Elective hip replacement (Imperiale & Speroff, 1994)[11]	25	1436	57**(4%)	3.0 to 5.1%
Traumatic orthopaedic surgery) (APTC,1994)[170]	11	494	34(6,9%)	4.8 to 9.5%

* In most of the studies using an objective method of screening for DVT, patients found to have proximal thrombosis were treated with anticoagulants; the true incidence of clinical pulmonary embolism in series without such screening and intervention is unknown.

** This number is an estimate from the percentage given in the paper.

Table IV

The frequency of fatal pulmonary embolism without prophylaxis.*

Patient groups	Number of Studies	Patients n	Incidence of fatal PE	95% CI
General surgery (Clagett & Reisch, 1988)[46]	33	5547	48(0.87%)	0.62% to 1.1%
Elective hip replacement (Collins et al, 1988)[47]	12	485	8(1.65%)	0.38% to 2.7%
Fractured neck of femur (Lassen & Borris, 1994)[171]	23	1195	48(4.0%)	3.0% to 5.3%

* In most of the studies using an objective method of screening for DVT, patients found to have proximal thrombosis were treated with anticoagulants; the true incidence of fatal pulmonary embolism in the absence of intervention is unknown.

Table V

Mortality after elective hip replacement in the absence of routine pharmacological prophylaxis.

Author	Number of Patients	Follow-up	Total deaths	95% CI	Fatal PE	95% CI	Anti-coagulant use
Seagroatt et al 1991[172]	11600	90 days	93 (1.10%)	0.87 to 1.31%	-	-	Very low
Sheppeard et al 1981[173]	3016	Inpatient	19 (0.63%)	0.38 to 0.98%	12 (0.40%)	0.20 to 0.70%	20%*
Warwick et al 1995[174]	1162**	90 days	15 (1.30%)	0.73 to 2.10%	4 (0.34%)	0.09 to 0.90%	11%*
Wroblewski et al 1992[175] et al 1992	18104	1 year	362 (2.0%)	1.80 to 2.20%	1.27 (0.70%)	0.58 to 0.82%	-
Fender et al 1997[176]	2111	42 days	19 (0.91%)	0.05 to 1.42%	4 (0.19%)	0.05 to 0.49	65%

* High risk patients received anticoagulation
** All patients wore thigh-length elastic stockings
- Information not available.

Table VI

The definition of risk categories in general surgical patients using FUT and in hospital pulmonary embolism (modified from Salzman and Hirsh, 1982)179124. Although based on old studies the percentages shown in this table are still used to define the category of risk.

Category	Frequency of calf vein thrombosis	Frequency of proximal vein thrombosis	Frequency of Fatal PE
High-risk	40-80%	10-30%	>1%
Moderate-risk	10-40%	1-10%	0.1-1%
Low-risk	<10%	<1%	<0.1%

Table VII

Risk categories according to clinical risk factors in non-orthopedic surgical patients

RISK CATEGORY	General Surgery	Gynaecology	Obstetrics*
HIGH			
	Major General Surgery, age >60	Major General Gynaecological Surgery, age >60	History of DVT/PE
	Major General Surgery, age 40-60 & cancer or history of DVT/PE	Major General Gynaecological Surgery, age 40-60 & cancer or history of DVT/PE	
	Thrombophilia	Thrombophilia	Thrombophilia
MODERATE			
	Major General Surgery, age 40-60 without other risk factors**	Major General Gynaecological Surgery, age 40-60	Age >35 years Caesarian section Obesity
	Minor surgery, age > 60	Major Gynaecological Surgery, age <40 on oestrogen therapy	
LOW			
	Minor surgery, age 40-60 with history of DVT/PE or on oestrogen therapy	Minor surgery, age > 60	
	Surgery, age <40 No other risk factors**	Minor Gynaecological surgery, age <40 without any other risk factors**	Age >35 years without any risk factors
	Minor surgery age 40-60 No other risk factors**	Minor Gynaecological surgery, age 40-60 without any other risk factors**	

* The risk of DVT in obstetric patients with pre-eclampsia and the other factors is unknown but prophylaxis should be considered.
** The risk is increased by infectious disease, presence of varicose veins, general immobility.

Minor surgery: Operations other than abdominal lasting less than 45 minutes
Major surgery: Any intra-abdominal operation and all other operations lasting more than 45 minutes.

Table VIII

Effect of graduated elastic compression stockings (GEC) in the prevention of DVT diagnosed by surveillance with objective methods in non-orthopedic surgical randomised controlled studies (fibrinogen uptake and/or phlebography)

Patient groups	Control Groups		Graduated Compression Stockings	
Author	**Number of patients**	**DVT (%)**	**Number of patients**	**DVT (%)**
Allan et al, 1983[245] Gen surgery	103	37 (36)	97	15 (15)
Borow & Goldson, 1981[246] Various surgical	89	32 (36)	91	14 (15)
Holford, 1976[247] Major surg	48	23 (48)	47	11 (23)
Scurr et al, 1977[248] Gen surgery	70	26 (37)	70	8 (11%)
Tsapogas et al, 1971[249] Gen surgery	44	6 (14)	54	2 (4)
Turner et al, 1984[250] Gynaec surg	92	4 (4)	104	0 (0)
Inada et al, 1983[251] Abdominal Surg	110	16 (14.5)	110	4 (3.6)
Turpie et al, 1989[126] Neurosurgery	81	16 (20)	80	7 (9)
Overall	**637**	**160 (25)**	**653**	**61 (9)**

Relative risk: 0.37 (95% CI 0.28 to 0.49)

Table IX

Effect of intermittent pneumatic compression (IPC) in the prevention of DVT diagnosed by surveillance with objective methods in non-orthopedic surgical randomized controlled studies (fibrinogen uptake test or phlebography)

	Control Groups		Intermittent Pneumatic Compression	
Author	**Number of patients**	**DVT (%)**	**Number of patients**	**DVT (%)**
Borow & Goldson, 1981[246]	89	32 (36)	79	9 (11)
Butson, 1981[255]	57	4 (7)	62	6 (10)
Clark et al, 1974[256*]	36	7 (19)	37	1 (3)
Clarke-Pearson et al, 1984[257]	52	18 (35)	55	7 (13)
Coe et al, 1978[112]	24	6 (25)	29	2 (7)
Hills et al, 1972[258]	50	15 (30)	50	6(12)
Roberts & Cotton, 1974[259]	104	27 (26)	94	6 (6)
Sabri et al, 1971[260*]	39	12 (31)	39	2 (5)
Skillman et al, 1978[123]	48	12 (25)	47	4 (9)
Turpie et al, 1977[124]	96	20 (21)	103	8 (8)
Turpie et al, 1979[261]	63	12 (19)	65	1 (2)
Overall	**658**	**165 (26)**	**660**	**52 (8)**

Relative risk: 0.31 (95% CI 0.33 to 0.42)

*Contralateral leg was used as the control

Table X

Effect of antiplatelet therapy (e.g. aspirin) in the prevention of DVT diagnosed by surveillance with objective methods (fibrinogen uptake in general surgery and phlebography in orthopedic surgery) in randomized controlled studies (Antiplatelet Trialists' Collaboration, 1994).[170]

Type of patient	Control Groups*					Antiplatelet Groups	
	Number of trials with data	Patients n	DVT (%)	Patients n	DVT (%)	RR	95%CI
General surgery	22	1459	396 (27)	1434	278 (19)	0.71	0.62 to 0.82
Orthopedic Traumatic	10	444	186 (42)	454	163 (36)	0.86	0.73 to 1.0
Orthopedic Elective	13	436	232 (53)	427	160 (37)	0.70	0.61 to 0.82
High risk medical	8	266	61 (23)	261	39 (15)	0.65	0.45 to 0.94

*In most trials patients were allocated evenly to antiplatelet therapy or control, but in some more were deliberately allocated to active treatment. To allow direct comparison between percentages adjusted control totals were calculated, (actual DVT incidence in surgical controls 700/2050; all medical trials evenly balanced).

Table XI

Effect of antiplatelet therapy (e.g. aspirin) in the prevention of PE in randomized controlled studies (Antiplatelet Trialists' Collaboration, 1994).[170 .170,262]

Type of patient	Control Groups*					Antiplatelet Groups	
	Number of trials with data	Number of Patients	PE	Number of Patients	PE	RR	95%CI
General surgery	26	3419	58(1.7%)	3408	16(0.5%)	0.28	0.16 to 0.48
Orthopedic Traumatic	11	494	34(6.9%)	504	14(2.8%)	0.40	0.22 to 0.71
Orthopedic Elective	16	537	29(5.4%)	529	14(2.6%)	0.49	0.26 to 0.92
High risk medical	9	280	8(2.9%)	275	3(1.1%)	0.38	0.10 to 1.42

*In most trials patients were allocated evenly to antiplatelet therapy or control, but in some more were deliberately allocated to active treatment. To allow direct comparison between percentages adjusted control totals were calculated, (actual DVT incidence in surgical controls 700/2050; all medical trials evenly balanced).

Table XII

Effect of low dose heparin (LDH) versus low dose heparin (LDH) and graduated elastic compression (GEC) in the prevention of DVT in non-orthopedic surgical patients diagnosed by surveillance with objective methods (fibrinogen uptake test and/or phlebography).

	GEC		LDH & GEC		
Author	**Number of patients**	**DVT**	**Number of patients**	**DVT**	**Surgical Procedure**
Borow & Goldson, 1983[263]	106	15(14%)	63	2(3%)	General surgery & Orthopedics
Moser & Froidevaux, 1976[264]	20	5(25%)	20	2(10%)	General surgery
Nicolaides et al, 1972[116]	122	29(24%)	122	1(1%)	Prostatectomy
Rasmussen et al, 1988[265]	74	22(30%)	89	23(26%)	General surgery
Overall	**322**	**71(22%)**	**294**	**28(9.5%)**	

Relative risk: 0.47 (95% CI 0.33 to 0.69)

Table XIII

Effect of low dose heparin (LDH) versus low dose heparin (LDH) and graduated elastic compression (GEC) in the prevention of DVT in non-orthopedic surgical patients diagnosed by surveillance with objective methods (fibrinogen uptake test and/or phlebography).

	LDH		LDH & GEC	
Author	**Number of patients**	**DVT**	**Number of patients**	**DVT**
Borow & Goldson, 1983[263]	86	23 (26%)	63	2 (3%)
Moser & Froidevaux, 1976[264]	15	0	20	2 (10%)
Rasmussen et al, 1988[265]	85	25 (29%)	89	23 (26%)
Torngren 1980[266]	98	12 (12%)	98	4 (4%)
Wille-Jorgensen et al, 1985[267]	86	11 (13%)	90	2 (2%)
Wille-Jorgensen et al, 1991[268]	81	12 (15%)	79	2 (3%)
Overall	**451**	**83 (18%)**	**439**	**35 (8%)**

Relative risk: 0.47 (95% CI 0.33 to 0.69)

Table XIV

Recommended management strategies for various clinical situations. (NB. specialist advice for individualized management of patients is advisable in many of these situations)

Clinical Situation	Recommended Management
Single previous VTE (not pregnancy or 'pill' related) associated with a transient risk factor and no additional current risk factors, such as obesity.	**Antenatal:** surveillance or prophylactic doses of LMWH ± CEG stockings. Discuss decision regarding antenatal LMWH with the woman. **Postpartum:** anticoagulant therapy for at least 6 weeks ± GEC stockings.
Single previous **idiopathic** VTE or pregnancy or COC related previous VTE or VTE with underlying thrombophilia and not on long-term anticoagulant therapy, or single previous VTE and additional current risk factor(s) (eg morbid obesity, nephrotic syndrome).	**Antenatal:** prophylactic doses of LMWH ± GEC stockings. NB: there is a strong case for more intense LMWH therapy in antithrombin deficiency **Postpartum:** anticoagulant therapy for at least 6 weeks ± GEC stockings.
More than one previous episode of VTE, with no thrombophilia and not on long-term anticoagulant therapy	**Antenatal:** prophylactic doses of LMWH + GEC stockings. **Postpartum:** anticoagulant therapy for at least 6 weeks + GEC stockings.
Previous episode(s) of VTE in women receiving long-term anticoagulants (eg with underlying thrombophilia)	**Antenatal:** switch from oral anticoagulants to LMWH therapy before 6 weeks gestation + GEC stockings. **Postpartum:** resume long-term anticoagulants with LMWH overlap until INR in pre-pregnancy therapeutic range + GEC stockings.
Thrombophilia (confirmed laboratory abnormality) but no prior VTE.	**Antenatal:** surveillance or prophylactic LMWH ± GEC stockings. The indication for LMWH in the antenatal period is stronger in AT deficient, women than the other thrombophilias, in symptomatic kindred compared to asymptomatic kindred and also where additional risk factors are present. **Postpartum:** anticoagulant therapy for at least 6 weeks ± GEC stockings.
Following caesarean section	Carry out risk assessment for VTE. If an additional risk factor such as emergency section in labour, age over 35 years, high BMI etc present provide thromboprophylaxis at least until discharge from hospital *
Following vaginal delivery.	Carry out risk assessment for VTE. If two or more additional risk factors such as age over 35 years, high BMI etc present consider thromboprophylaxis ± GEC stockings at least until discharge from hospital*.

*** NB where multiple risk factors are present consider extended prophylaxis after discharge.**

Table XV

Guidelines for antenatal prophylactic and therapeutic doses of LMWH (RCOG 2004[310])

Prophylaxis	Prophylaxis	Enoxaparin (100 units/mg)	Tinzaparin*
Normal body Weight	40 mg daily	5000 units daily	4500 units daily
Body weight < 50 kg	20 mg daily	2500 units daily	3500 units daily
Body weight >90 kg	40 mg 12 hourly	5000 units12hourly	4500 units12-hourly
Therapeuticy dose	1mg/kg 12 hourly	90units/kg 12-hourly	90units/kg 12-hourly

*Recent reports recommend Tinzaparin in daily dosage of 75units/kg for prophylaxis and 175units/kg for therapeutic dosage in pregnancy

Table XVI

Effect of intermittent pneumatic compression (IPC) in the prevention of DVT diagnosed by surveillance with phlebography or duplex ultrasound* (Fisher et al, 1995)[343] in randomized controlled studies of orthopedic patients

	Control Groups (No prophylaxis)		IPC		Procedure
Author	**Number of patients**	**DVT (%)**	**Number of patients**	**DVT (%)**	
A. HIP REPLACEMENT					
Gallus et al, 1983[64]	47	25 (53.2)	43	15 (34.9)	Hip (elective)
Hartman et al, 19823[344]	52	10 (19)	53	1 (1.9)	Hip (elective & fracture)
Hull et al, 1990[68]	158	77 (49)	152	36 (24)	Hip (elective)
Overall	**257**	**112 (43.6)**	**248**	**52 (21.0)**	
Relative risk: 0.48 (95% CI 0.36 to 0.64)					
B. KNEE REPLACEMENT					
Haas et al, 1990[345]	36 (Aspirin)	17 (47)	36	8 (22)	
Hull et al, 1979[80]	29	19 (65.5)	32	2 (6.3)	
Overall	**65**	**36 (55.4)**	**68**	**10 (14.7.0)**	
Relative risk: 0.27 (95% CI 0.14 to 0.49)					

Table XVII

Effect of prophylaxis using the combination of foot impulse technology (FIT) with graduated elastic compression (GEC) on proximal DVT, in orthopedic patients

Author and diagnostic method	Control Method of prophylaxis			Foot Impulse Technology plus Additional method of prophylaxis	
		n	Proximal DVT	n	Proximal DVT
Hip surgery					
Bradley et al, 1993[346] VG	GEC	44	11(25%)	30	2(6.7%)
Fordyce & Ling 1992[347] VG	GEC	40	13(32%)	39	2(5%)
Santori et al, 1994[348] US	LDUH	65	13(20%)	67	2(3.0%)
Warwick et al, 1998[349] VG	LMWH +GEC	138	27(17.4%)	136	12(9%)
Pitto et al, 2004[350] US	LMWH	100	6(6%)	100	3(3%)
Knee surgery					
Blanchard et al,1999[351] VG	LMWH	60	2(3.3%)	48	4(8.3%)
Wilson et al, 1992[86] VG	Nil	23	6(19%)	28	0
Westrich et al, 1996[342] VG	Aspirin	83	49(59%)	81	22 (27%)
Warwick et al, 2002[352] VG	LMWH	99	57(58%)	98	48(54%)
Hip fracture					
Stranks et al, 1992[353] US	GEC	39	9(23%)	41	0

VG: Venography; US: Ultrasound

Table XVIII

Effect of warfarin versus low molecular weight heparin (LMWH) in the prevention of DVT diagnosed by surveillance with phlebography in patients having knee surgery.

	Warfarin		LMWH	
Author	**Number of patients**	**DVT**	**Number of patients**	**DVT**
Heit et al, 1997[354]	222	85 (38%)	231	62 (27%)
Hull et al, 1993[355]	277	152 (55%)	258	116 (45%)
Leclerc et al, 1996[82]	211	109 (52%)	206	76 (37%)
RDHAG 1994[356]	147	60 (41%)	299	78 (26%)
Fitzgerald et al, 2001[357]	176	80 (45%)	173	44 (25%)
Hamulyak et al, 1995[358]	61	23 (38%)	65	16 (25%)
Overall	1033	**486 (47%)**	**1167**	**376 (32%)**

Relative risk: 0.68 (95% CI 0.62 to 0.76)

TABLE XIX

Incidence of thrombosis in early-stage breast cancer

Study	Treatment	Number of Patient	Patient with thrombosis %
Node-Negative			
Fisher 1990[516]	T	1318	0.9
	Placebo	1326	0.15
	CMFT	768	4.2
	T	771	0.8
Node-Positive			
Levine 1988[478]	CMFVP	102	8.8
	CMFVP + AT	103	4.9
Pritchard 1996[517]	CMF + T	353	9.6
	T	352	1.4
Clahsen 1994[519]	Perioperative FAC	1292	2.1
Rivkin 1994[521]	No Rx	1332	0.8
	CMFVP + T	303	3.6
	CMFVP	300	1.3
Fisher 1990[516]	T	295	0
	ACT	383	3.1
Weiss 1981[518]	T	367	1.6
	CMFVP	143	6.3
	CMF	144	3.5

A indicates adriamycin; C, cyclophosphamide; F, fluorouracil; M, methotrexate; P, prednisone, T, tamoxifen; V, vincristine

TABLE XX

Incidence of thrombosis in patients with different tumors

Study	Tumour	Patient Number	Thrombosis (%)
Brandes et al, 1997[467]	Malignant glioma	75	24.0
Weijl et al, 2000[522]	Germ cell	179	8.4
Ottinger et al, 1995[523]	Non-Hodgkins Lymphoma	593	6.6
Clarke et al, 1990[524]	Non-Hodgkins Lymphoma	85	4.7
Von Tempelhoff et al, 2000[525]	Ovarian	47	10.6

TABLE XXI

Major bleeding complication rate according to INR intensity

Trial	INR Range	Event Rate per 100 person-years
Kearon, et al, 1999[630]	2.0-3.0	3.8
Schulman et al, 1997[575]	2.0-2.85	2.4
Kearon et al, 2003[631]	2.0-3.0	0.9
Kearon et al, 2003[631]	1.5-1.9	1.1
Ridker et al, 2003[632]	1.5-2.0	0.9

References

1. Nicolaides AN, Arcelus J, Belcaro G, Bergqvist D, Borris LC, Buller HR, et al. Prevention of venous thromboembolism. European Consensus Statement, 1-5 November 1991, developed at Oakley Court Hotel, Windsor, UK. Int Angiol. 1992;11:151-9.
2. Prevention of venous thromboembolism. International Consensus Statement (guidelines according to scientific evidence). Int Angiol. 1997;16:3-38.
3. Nicolaides AN, Breddin HK, Fareed J, Goldhaber S, Haas S, Hull R, et al. Prevention of venous thromboembolism. International Consensus Statement. Guidelines compiled in accordance with the scientific evidence. Int Angiol. 2001;20:1-37.
4. Scottish Intercollegiate Guidelines Network Prophylaxis of Venous Thromboembolism. October 2002.
5. McAlister FA, Straus SE, Guyatt GH, Haynes RB. Users' guides to the medical literature: XX. Integrating research evidence with the care of the individual patient. Evidence-Based Medicine Working Group. JAMA. 2000;283:2829-36.
6. McAlister FA, Clark HD, van Walraven C, Straus SE, Lawson FM, Moher D, et al. The medical review article revisited: has the science improved? Ann Intern Med. 1999;131:947-51.
7. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. 1999;354:1896-900.
8. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:338S-400S.
9. Colditz GA, Tuden RL, Oster G. Rates of venous thrombosis after general surgery: combined results of randomised clinical trials. Lancet. 1986;2:143-6.
10. Mohr DN, Silverstein MD, Murtaugh PA, Harrison JM. Prophylactic agents for venous thrombosis in elective hip surgery. Meta-analysis of studies using venographic assessment. Arch Intern Med. 1993;153:2221-8.
11. Imperiale TF, Speroff T. A meta-analysis of methods to prevent venous thromboembolism following total hip replacement. JAMA. 1994;271:1780-5.
12. Kakkar VV. The problems of thrombosis in the deep veins of the leg. Ann R Coll Surg Engl. 1969;45:257-76.
13. Philbrick JT, Becker DM. Calf deep venous thrombosis. A wolf in sheep's clothing? Arch Intern Med. 1988;148:2131-8.
14. Hull RD, Hirsh J, Carter CJ, Jay RM, Dodd PE, Ockelford PA, et al. Pulmonary angiography, ventilation lung scanning, and venography for clinically suspected pulmonary embolism with abnormal perfusion lung scan. Ann Intern Med. 1983; 98:891-9.
15. Hull RD, Pineo GF, Stein PD, Mah AF, MacIsaac SM, Dahl OE, et al. Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. Ann Intern Med. 2001;135:858-69.
16. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. Lancet. 2001;358:9-15.

17. Wille-Jorgensen P, Jorgensen LN, Crawford M. Asymptomatic postoperative deep vein thrombosis and the development of postthrombotic syndrome. A systematic review and meta-analysis. Thromb Haemost. 2005;93:236-41.
18. Lindblad B, Sternby NH, Bergqvist D. Incidence of venous thromboembolism verified by necropsy over 30 years. BrMedJ. 1991;302:709-11.
19. Lindblad B, Eriksson A, Bergqvist D. Autopsy-verified pulmonary embolism in a surgical department: analysis of the period from 1951 to 1988. Br J Surg. 1991;78:849-52.
20. Anderson FA, Jr., Wheeler HB, Goldberg RJ, Hosmer DW, Forcier A. The prevalence of risk factors for venous thromboembolism among hospital patients. Arch Intern Med. 1992;152:1660-4.
21. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med. 1992;232:155-60.
22. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. Arch Intern Med. 1999;159:445-53.
23. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med. 2000;160:809-15.
24. Nelzen O, Bergqvist D, Lindhagen A, Hallbook T. Chronic leg ulcers: an underestimated problem in primary health care among elderly patients. J Epidemiol Community Health. 1991;45:184-7.
25. Nelzen O, Bergqvist D, Lindhagen A. Leg ulcer etiology—a cross sectional population study. J Vasc Surg. 1991;14:557-64.
26. Jantet G. The socioeconomic impact of venous pathology in Great Britain. Phlebologie. 1992;45:433-7.
27. Ruckley CV. Socioeconomic impact of chronic venous insufficiency and leg ulcers. Angiology. 1997;48:67-9.
28. McGuckin M, Waterman R, Brooks J, Cherry G, Porten L, Hurley S, et al. Validation of venous leg ulcer guidelines in the United States and United Kingdom. Am J Surg. 2002;183:132-7.
29. Kearon C. Epidemiology of venous thromboembolism. Sem Vasc Med. 2001;1:7-25.
30. Kakkar VV, Howe CT, Nicolaides AN, Renney JT, Clarke MB. Deep vein thrombosis of the leg. Is there a "high risk" group? Am J Surg. 1970;120:527-30.
31. Clayton JK, Anderson JA, McNicol GP. Preoperative prediction of postoperative deep vein thrombosis. Br Med J. 1976;2:910-2.
32. Havig O. Deep vein thrombosis and pulmonary embolism. An autopsy study with multiple regression analysis of possible risk factors. Acta Chir Scand Suppl. 1977;478:1-120.
33. Lowe GD, Carter DC, Prentice CR. Preoperative prediction of postoperative deep-vein thrombosis. Lancet. 1982;1:1474.
34. Sue-Ling HM, Johnston D, McMahon MJ, Philips PR, Davies JA. Pre-operative identification of patients at high risk of deep venous thrombosis after elective major abdominal surgery. Lancet. 1986;1:1173-6.
35. Campbell B. Thrombosis, phlebitis, and varicose veins. BrMedJ. 1996;312:198-9.
36. Daly E, Vessey MP, Painter R, Hawkins MM. Case-control study of venous thromboembolism risk in users of hormone replacement therapy. Lancet. 1996;348:1027.

37. Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of venous thromboembolism in users of hormone replacement therapy. Lancet. 1996;348:977-80.
38. Goldhaber SZ, Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, et al. A prospective study of risk factors for pulmonary embolism in women. JAMA. 1997;277:642-5.
39. Lowe GD, Haverkate F, Thompson SG, Turner RM, Bertina RM, Turpie AG, et al. Prediction of deep vein thrombosis after elective hip replacement surgery by preoperative clinical and haemostatic variables: the ECAT DVT Study. European Concerted Action on Thrombosis. Thromb Haemost. 1999;81:879-86.
40. Nicolaides AN. Thrombophilia and venous thromboembolism. International Consensus Statement. Guidelines According to Scientific Evidence. Int Angiol. 2005;24:1-26.
41. Scurr JH, Coleridge-Smith PD, Hasty JH. Deep venous thrombosis: a continuing problem. Br Med J. 1988;297:28.
42. White RH, Gettner S, Newman JM, Trauner KB, Romano PS. Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. N Engl J Med. 2000;343:1758-64.
43. Vaitkus PT, Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Goldhaber SZ. Mortality rates and risk factors for asymptomatic deep vein thrombosis in medical patients. Thromb Haemost. 2005;93:76-9.
44. Kucher N, Koo S, Quiroz R, Cooper JM, Paterno MD, Soukonnikov B, et al. Electronic alerts to prevent venous thromboembolism among hospitalized patients. N Engl J Med. 2005;352:969-77.
45. Bergentz SE. Dextran in the prophylaxis of pulmonary embolism. World J Surg. 1978;2:19-25.
46. Clagett GP, Reisch JS. Prevention of venous thromboembolism in general surgical patients. Results of meta-analysis. Ann Surg. 1988;208:227-40.
47. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. N Engl J Med. 1988;318:1162-73.
48. Gallus AS. Anticoagulants in the prevention of venous thromboembolism. Baillieres Clin Haematol. 1990;3:651-84.
49. Bergqvist D, Lindblad B. Incidence of venous thromboembolism in medical and surgical patients. In: Bergqvist D, Comerota A, Nicolaides A, Scurr J, eds. Prevention of venous thromboembolism. London: Med-Orion Publ Comp; 1994:3-15.
50. Czechanowski B, Heinrich F. [Prevention of venous thrombosis in recent ischaemic cerebrovascular accident: double-blind study with heparin-dihydroergotamine (author's transl)]. Dtsch Med Wochenschr. 1981;106:1254-60.
51. Dahan R, Houlbert D, Caulin C, Cuzin E, Viltart C, Woler M, et al. Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: a randomized double-blind trial. Haemostasis. 1986;16:159-64.
52. Elias A, Milandre L, Lagrange G, Aillaud MF, Alonzo B, Toulemonde F, et al. Prevention of deep venous thrombosis of the leg by a very low molecular weight heparin fraction (CY 222) in patients with hemiplegia following cerebral infarction: a randomized pilot study (30 patients). Rev Med Interne. 1990;11:95-8.
53. McCarthy ST, Turner JJ, Robertson D, Hawkey CJ, Macey DJ. Low-dose heparin as a

prophylaxis against deep-vein thrombosis after acute stroke. Lancet. 1977;2:800-1.
54. McCarthy ST, Turner J. Low-dose subcutaneous heparin in the prevention of deep-vein thrombosis and pulmonary emboli following acute stroke. Age Ageing. 1986;15:84-8.
55. Prins MH, Gelsema R, Sing AK, van Heerde LR, den Ottolander GJ. Prophylaxis of deep venous thrombosis with a low-molecular-weight heparin (Kabi 2165/Fragmin) in stroke patients. Haemostasis. 1989;19:245-50.
56. Sandset PM, Dahl T, Stiris M, Rostad B, Scheel B, Abildgaard U. A double-blind and randomized placebo-controlled trial of low molecular weight heparin once daily to prevent deep-vein thrombosis in acute ischemic stroke. Semin Thromb Hemost. 1990;16 Suppl:25-33.
57. Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, et al. Double-blind randomised trial of Org 10172 low-molecular-weight heparinoid in prevention of deep-vein thrombosis in thrombotic stroke. Lancet. 1987;1:523-6.
58. Warlow C, Ogston D, Douglas AS. Venous thrombosis following strokes. Lancet. 1972;1:1305-6.
59. Belch JJ, Meek DR, Lowe GD, Campbell AF, Young AB, Forbes CD, et al. Subcutaneous ancrod in prevention of deep vein thrombosis after hip replacement surgery. Thromb Res. 1982;25:23-31.
60. Bergqvist D, Efsing HO, Hallbook T, Hedlund T. Thromboembolism after elective and post-traumatic hip surgery—a controlled prophylactic trial with dextran 70 and low-dose heparin. Acta Chir Scand. 1979;145:213-8.
61. Dechavanne M, Saudin F, Viala JJ, Kher A, Bertrix L, de Mourgues G. Prevention of venous thrombosis. Success of high doses of heparin during total hip replacement for osteoarthritis. Nouv Presse Med. 1974;3:1317-9.
62. Dechavanne M, Ville D, Viala JJ, Kher A, Faivre J, Pousset MB, et al. Controlled trial of platelet anti-aggregating agents and subcutaneous heparin in prevention of postoperative deep vein thrombosis in high risk patients. Haemostasis. 1975;4:94-100.
63. Evarts CM, Feil EJ. Prevention of thromboembolic disease after elective surgery of the hip. J Bone Joint Surg Am. 1971;53:1271-80.
64. Gallus A, Raman K, Darby T. Venous thrombosis after elective hip replacement—the influence of preventive intermittent calf compression and of surgical technique. Br J Surg. 1983;70:17-9.
65. Hampson WG, Harris FC, Lucas HK, Roberts PH, McCall IW, Jackson PC, et al. Failure of low-dose heparin to prevent deep-vein thrombosis after hip-replacement arthroplasty. Lancet. 1974;2:795-7.
66. Harris WH, Salzman EW, Athanasoulis CA, Waltman AC, DeSanctis RW. Aspirin prophylaxis of venous thromboembolism after total hip replacement. N Engl J Med. 1977;297:1246-9.
67. Hoek JA, Nurmohamed MT, Hamelynck KJ, Marti RK, Knipscheer HC, ten Cate H, et al. Prevention of deep vein thrombosis following total hip replacement by low molecular weight heparinoid. Thromb Haemost. 1992;67:28-32.
68. Hull RD, Raskob GE, Gent M, McLoughlin D, Julian D, Smith FC, et al. Effectiveness of intermittent pneumatic leg compression for preventing deep vein thrombosis after total hip replacement. JAMA. 1990;263:2313-7.
69. Ishak MA, Morley KD. Deep venous thrombosis after total hip arthroplasty: a prospective controlled study to determine the prophylactic effect of graded pressure stockings. Br J

Surg. 1981;68:429-32.
70. Kalodiki EP, Hoppensteadt DA, Nicolaides AN, Fareed J, Gill K, Regan F, et al. Deep venous thrombosis prophylaxis with low molecular weight heparin and elastic compression in patients having total hip replacement. A randomised controlled trial. Int Angiol. 1996;15:162-8.
71. Mannucci PM, Citterio LE, Panajotopoulos N. Low-dose heparin and deep-vein thrombosis after total hip replacement. Thromb Haemost. 1976;36:157-64.
72. Morris GK, Henry AP, Preston BJ. Prevention of deep-vein thrombosis by low-dose heparin in patients undergoing total hip replacement. Lancet. 1974;2:797-800.
73. Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, et al. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery. N Engl J Med. 1986;315:925-9.
74. Venous Thrombosis Clinical Study Group. Small doses of subcutaneous sodium heparin in the prevention of deep vein thrombosis after elective hip operations. Br J Surg. 1975;62:348-50.
75. Welin-Berger T, Bygdeman S, Mebius C. Deep vein thrombosis following hip surgery. Relation to activated factor X inhibitor activity: effect of heparin and dextran. Acta Orthop Scand. 1982;53:937-45.
76. Freeark RJ, Boswick J, Fardin R. Posttraumatic venous thrombosis. Arch Surg. 1967;95:567-75.
77. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. N Engl J Med. 1994;331:1601-6.
78. Kudsk KA, Fabian TC, Baum S, Gold RE, Mangiante E, Voeller G. Silent deep vein thrombosis in immobilized multiple trauma patients. Am J Surg. 1989;158:515-9.
79. Shackford SR, Davis JW, Hollingsworth-Fridlund P, Brewer NS, Hoyt DB, Mackersie RC. Venous thromboembolism in patients with major trauma. Am J Surg. 1990;159:365-9.
80. Hull R, Delmore TJ, Hirsh J, Gent M, Armstrong P, Lofthouse R, et al. Effectiveness of intermittent pulsatile elastic stockings for the prevention of calf and thigh vein thrombosis in patients undergoing elective knee surgery. Thromb Res. 1979;16:37-45.
81. Kim YH. The incidence of deep vein thrombosis after cementless and cemented knee replacement. J Bone Joint Surg Br. 1990;72:779-83.
82. Leclerc JR, Geerts WH, Desjardins L, Laflamme GH, L'Esperance B, Demers C, et al. Prevention of venous thromboembolism after knee arthroplasty. A randomized, double-blind trial comparing enoxaparin with warfarin. Ann Intern Med. 1996;124:619-26.
83. Lynch AF, Bourne RB, Rorabeck CH, Rankin RN, Donald A. Deep-vein thrombosis and continuous passive motion after total knee arthroplasty. J Bone Joint Surg Am. 1988;70:11-4.
84. Stringer MD, Steadman CA, Hedges AR, Thomas EM, Morley TR, Kakkar VV. Deep vein thrombosis after elective knee surgery. An incidence study in 312 patients. J Bone Joint Surg Br. 1989;71:492-7.
85. Stulberg BN, Insall JN, Williams GW, Ghelman B. Deep-vein thrombosis following total knee replacement. An analysis of six hundred and thirty-eight arthroplasties. J Bone Joint Surg Am. 1984;66:194-201.
86. Wilson NV, Das SK, Kakkar VV, Maurice HD, Smibert JG, Thomas EM, et al. Thrombo-embolic prophylaxis in total knee replacement. Evaluation of the A-V Impulse System. J Bone Joint Surg Br. 1992;74:50-2.

87. Ahlberg A, Nylander G, Robertson B, Cronberg S, Nilsson IM. Dextran in prophylaxis of thrombosis in fractures of the hip. Acta Chir Scand Suppl. 1968;387:83-5.
88. Checketts RG, Bradley JG. Low-dose heparin in femoral neck fractures. Injury. 1974;6:42-4.
89. Darke SG. Ilo-femoral venous thrombosis after operations on the hip. A prospective controlled trial using dextran 70. J Bone Joint Surg Br. 1972;54:615-20.
90. Galasko CS, Edwards DH, Fearn CB, Barber HM. The value of low dosage heparin for the prophylaxis of thromboembolism in patients with transcervical and intertrochanteric femoral fractures. Acta Orthop Scand. 1976;47:276-82.
91. Gallus AS, Hirsh J, Tutle RJ, Trebilcock R, O'Brien SE, Carroll JJ, et al. Small subcutaneous doses of heparin in prevention of venous thrombosis. N Engl J Med. 1973;288:545-51.
92. Kakkar VV, Corrigan T, Spindler J, Fossard DP, Flute PT, Crellin RQ, et al. Efficacy of low doses of heparin in prevention of deep-vein thrombosis after major surgery. A double-blind, randomised trial. Lancet. 1972;2:101-6.
93. Lahnborg G. Effect of low-dose heparin and dihydroergotamine on frequency of postoperative deep-vein thrombosis in patients undergoing post-traumatic hip surgery. Acta Chir Scand. 1980;146:319-22.
94. Montrey JS, Kistner RL, Kong AY, Lindberg RF, Mayfield GW, Jones DA, et al. Thromboembolism following hip fracture. J Trauma. 1985;25:534-7.
95. Morris GK, Mitchell JR. Warfarin sodium in prevention of deep venous thrombosis and pulmonary embolism in patients with fractured neck of femur. Lancet. 1976;2:869-72.
96. Morris GK, Mitchell JR. Preventing venous thromboembolism in elderly patients with hip fractures: studies of low-dose heparin, dipyridamole, aspirin, and flurbiprofen. Br Med J. 1977;1:535-7.
97. Myhre HO, Holen A. Thrombosis prophylaxis. Dextran or warfarin-sodium? A controlled clinical study. Nord Med. 1969;82:1534-8.
98. Powers PJ, Gent M, Jay RM, Julian DH, Turpie AG, Levine M, et al. A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. Arch Intern Med. 1989;149:771-4.
99. Rogers PH, Walsh PN, Marder VJ, Bosak GC, Lachman JW, Ritchie WG, et al. Controlled trial of low-dose heparin and sulfinpyrazone to prevent venous thromboembolism after operation on the hip. J Bone Joint Surg Am. 1978;60:758-62.
100. Svend-Hansen H, Bremerskov V, Gotrik J, Ostri P. Low-dose heparin in proximal femoral fractures. Failure to prevent deep-vein thrombosis. Acta Orthop Scand. 1981;52:77-80.
101. Xabregas A, Gray L, Ham JM. Heparin prophylaxis of deep vein thrombosis in patients with a fractured neck of the femur. Med J Aust. 1978;1:620-2.
102. Bors E, Conrad CA, Massell TB. Venous occlusion of lower extremities in paraplegic patients. Surg Gynecol Obstet. 1954;99:451-4.
103. Brach BB, Moser KM, Cedar L, Minteer M, Convery R. Venous thrombosis in acute spinal cord paralysis. J Trauma. 1977;17:289-92.
104. Rossi EC, Green D, Rosen JS, Spies SM, Jao JS. Sequential changes in factor VIII and platelets preceding deep vein thrombosis in patients with spinal cord injury. Br J Haematol. 1980;45:143-51.
105. Silver JR. The prophylactic use of anticoagulant therapy in the prevention of pulmonary emboli in one hundred consecutive spinal injury patients. Paraplegia. 1974;12:188-96.

106. Watson N. Anticoagulant therapy in the treatment of venous thrombosis and pulmonary embolism in acute spinal injury. Paraplegia. 1974;12:197-201.
107. Frisbie JH, Sasahara AA. Low dose heparin prophylaxis for deep venous thrombosis in acute spinal cord injury patients: a controlled study. Paraplegia. 1981;19:343-6.
108. Merli GJ, Herbison GJ, Ditunno JF, Weitz HH, Henzes JH, Park CH, et al. Deep vein thrombosis: prophylaxis in acute spinal cord injured patients. Arch Phys Med Rehabil. 1988;69:661-4.
109. Myllynen P, Kammonen M, Rokkanen P, Bostman O, Lalla M, Laasonen E. Deep venous thrombosis and pulmonary embolism in patients with acute spinal cord injury: a comparison with nonparalyzed patients immobilized due to spinal fractures. J Trauma. 1985;25:541-3.
110. Yelnik A, Dizien O, Bussel B, Schouman-Claeys E, Frija G, Pannier S, et al. Systematic lower limb phlebography in acute spinal cord injury in 147 patients. Paraplegia. 1991;29:253-60.
111. Becker J, Borgstrom S, Saltzman GF. Occurrence and course of thrombosis following prostatectomy. A phlebographic investigation. Acta Radiol Diagn (Stockh). 1970;10:513-33.
112. Coe NP, Collins RE, Klein LA, Bettmann MA, Skillman JJ, Shapiro RM, et al. Prevention of deep vein thrombosis in urological patients: a controlled, randomized trial of low-dose heparin and external pneumatic compression boots. Surgery. 1978;83:230-4.
113. Hedlund PO, Blomback M. The effects of low-dose heparin treatment on patients undergoing transvesical prostatectomy. Urol Res. 1981;9:147-52.
114. Kutnowski M, Vandendris M, Steinberger R, Kraytman M. Prevention of postoperative deep-vein thrombosis by low-dose heparin in urological surgery. A double-blind, randomised study. Urol Res. 1977;5:123-5.
115. Mayo ME, Halil T, Browse NL. The incidence of deep vein thrombosis after prostatectomy. Br J Urol. 1971;43:738-42.
116. Nicolaides AN, Field ES, Kakkar VV, Yates-Bell AJ, Taylor S, Clarke MB. Prostatectomy and deep-vein thrombosis. Br J Surg. 1972;59:487-8.
117. Vandendris M, Kutnowski M, Futeral B, Gianakopoulos X, Kraytman M, Gregoir W. Prevention of postoperative deep-vein thrombosis by low-dose heparin in open prostatectomy. Urol Res. 1980;8:219-21.
118. Williams HT. Prevention of postoperative deep-vein thrombosis with perioperative subcutaneous heparin. Lancet. 1971;2:950-2.
119. Hedlund PO. Postoperative venous thrombosis in benign prostatic disease. A study of 316 patients, using the 125I-fibrinogen uptake test. Scand J Urol Nephrol. 1975:1-100.
120. Moser KM, LeMoine JR, Nachtwey FJ, Spragg RG. Deep venous thrombosis and pulmonary embolism. Frequency in a respiratory intensive care unit. JAMA. 1981;246:1422-4.
121. Cade JF. High risk of the critically ill for venous thromboembolism. Crit Care Med. 1982;10:448-50.
122. Fraisse F, Holzapfel L, Couland JM, Simonneau G, Bedock B, Feissel M, et al. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. Am J Respir Crit Care Med. 2000;161:1109-14.
123. Skillman JJ, Collins RE, Coe NP, Goldstein BS, Shapiro RM, Zervas NT, et al. Prevention

of deep vein thrombosis in neurosurgical patients: a controlled, randomized trial of external pneumatic compression boots. Surgery. 1978;83:354-8.
124. Turpie AG, Gallus A, Beattie WS, Hirsh J. Prevention of venous thrombosis in patients with intracranial disease by intermittent pneumatic compression of the calf. Neurology. 1977;27:435-8.
125. Turpie AG, Gent M, Doyle DJ, Saerens E, de Boer AC, Talbot C, et al. An evaluation of suloctidil in the prevention of deep vein thrombosis in neurosurgical patients. Thromb Res. 1985;39:173-81.
126. Turpie AG, Hirsh J, Gent M, Julian D, Johnson J. Prevention of deep vein thrombosis in potential neurosurgical patients. A randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. Arch Intern Med. 1989;149:679-81.
127. Zelikovski A, Zucker G, Eliashiv A, Reiss R, Shalit M. A new sequential pneumatic device for the prevention of deep vein thrombosis. J Neurosurg. 1981;54:652-4.
128. Clarke-Pearson DL, Coleman RE, Synan IS, Hinshaw W, Creasman WT. Venous thromboembolism prophylaxis in gynecologic oncology: a prospective, controlled trial of low-dose heparin. Am J Obstet Gynecol. 1983;145:606-13.
129. Clarke-Pearson DL, Creasman WT, Coleman RE, Synan IS, Hinshaw WM. Perioperative external pneumatic calf compression as thromboembolism prophylaxis in gynecologic oncology: report of a randomized controlled trial. Gynecol Oncol. 1984;18:226-32.
130. Clark-Pearson DL, DeLong E, Synan IS, Soper JT, Creasman WT, Coleman RE. A controlled trial of two low-dose heparin regimens for the prevention of postoperative deep vein thrombosis. Obstet Gynecol. 1990;75:684-9.
131. Walsh JJ, Bonnar J, Wright FW. A study of pulmonary embolism and deep leg vein thrombosis after major gynaecological surgery using labelled fibrinogen-phlebography and lung scanning. J Obstet Gynaecol Br Commonw. 1974;81:311-6.
132. Emerson PA, Marks P. Preventing thromboembolism after myocardial infarction: effect of low-dose heparin or smoking. Br Med J. 1977;1:18-20.
133. Handley AJ. Low-dose heparin after myocardial infarction. Lancet. 1972;2:623-4.
134. Nicolaides AN, Kakkar VV, Renney JT, Kidner PH, Hutchison DC, Clarke MB. Myocardial infarction and deep-vein thrombosis. Br Med J. 1971;1:432-4.
135. Warlow C, Terry G, Kenmure AC, Beattie AG, Ogston D, Douglas AS. A double-blind trial of low doses of subcutaneous heparin in the prevention of deep-vein thrombosis after myocardial infarction. Lancet. 1973;2:934-6.
136. Hartsuck JM, Greenfield LJ. Postoperative thromboembolism. A clinical study with 125I-fibrinogen and pulmonary scanning. Arch Surg. 1973;107:733-9.
137. Angelides NS, Nicolaides AN, Fernandes J, Gordon-Smith I, Bowers R, Lewis JD. Deep venous thrombosis in patients having aorto-iliac reconstruction. Br J Surg. 1977;64: 517-8.
138. Belch JJ, Lowe GD, Pollock JG, Forbes CD, Prentice CR. Low dose heparin in the prevention of deep-vein thrombosis after aortic bifurcation graft surgery. Thromb Haemost. 1980;42:1429-33.
139. Olin JW, Graor RA, O'Hara P, Young JR. The incidence of deep venous thrombosis in patients undergoing abdominal aortic aneurysm resection. J Vasc Surg. 1993;18:1037-41.
140. Killewich LA, Aswad MA, Sandager GP, Lilly MP, Flinn WR. A randomized, prospective trial of deep venous thrombosis prophylaxis in aortic surgery. Arch Surg. 1997;132:499-504.

141. Hollyoak M, Woodruff P, Muller M, Daunt N, Weir P. Deep venous thrombosis in postoperative vascular surgical patients: a frequent finding without prophylaxis. J Vasc Surg. 2001;34:656-60.
142. Hamer JD. Investigation of oedema of the lower limb following successful femoropopliteal by-pass surgery: the role of phlebography in demonstrating venous thrombosis. Br J Surg. 1972;59:979-82.
143. Passman MA, Farber MA, Marston WA, Carlin RE, Owens LV, Burnham CB, et al. Prospective screening for postoperative deep venous thrombosis in patients undergoing infrainguinal revascularization. J Vasc Surg. 2000;32:669-75.
144. Hjelmstedt A, Bergvall U. Incidence of thrombosis in patients with tibial fractures. Acta Chir Scand. 1968;134:209-18.
145. Abelseth G, Buckley RE, Pineo GE, Hull R, Rose MS. Incidence of deep-vein thrombosis in patients with fractures of the lower extremity distal to the hip. J Orthop Trauma. 1996;10:230-5.
146. Kujath P, Spannagel U, Habscheid W. Incidence and prophylaxis of deep venous thrombosis in outpatients with injury of the lower limb. Haemostasis. 1993;23 Suppl 1:20-6.
147. Kock HJ, Schmit-Neuerburg KP, Hanke J, Rudofsky G, Hirche H. Thromboprophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. Lancet. 1995;346:459-61.
148. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. N Engl J Med. 2002;347:726-30.
149. Jorgensen PS, Warming T, Hansen K, Paltved C, Vibeke Berg H, Jensen R, et al. Low molecular weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venografic controlled study. Thromb Res. 2002;105:477-80.
150. Ballard RM, Bradley-Watson PJ, Johnstone FD, Kenney A, McCarthy TG. Low doses of subcutaneous heparin in the prevention of deep vein thrombosis after gynaecological surgery. J Obstet Gynaecol Br Commonw. 1973;80:469-72.
151. Bonnar J, Walsh J. Prevention of thrombosis after pelvic surgery by British dextran 70. Lancet. 1972;1:614-6.
152. Taberner DA, Poller L, Burslem RW, Jones JB. Oral anticoagulants controlled by the British comparative thromboplastin versus low-dose heparin in prophylaxis of deep vein thrombosis. Br Med J. 1978;1:272-4.
153. West JL, 3rd, Anderson LD. Incidence of deep vein thrombosis in major adult spinal surgery. Spine. 1992;17:S254-7.
154. Oda T, Fuji T, Kato Y, Fujita S, Kanemitsu N. Deep venous thrombosis after posterior spinal surgery. Spine. 2000;25:2962-7.
155. Belch JJ, Lowe GD, Ward AG, Forbes CD, Prentice CR. Prevention of deep vein thrombosis in medical patients by low-dose heparin. Scott Med J. 1981;26:115-7.
156. Prescott SM, Richards KL, Tikoff G, Armstrong JD, Jr., Shigeoka JW. Venous thromboembolism in decompensated chronic obstructive pulmonary disease. A prospective study. Am Rev Respir Dis. 1981;123:32-6.
157. Schonhofer B, Kohler D. Prevalence of deep-vein thrombosis of the leg in patients with acute exacerbation of chronic obstructive pulmonary disease. Respiration. 1998;65:173-7.
158. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A, Janbon C, et al. A

comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. N Engl J Med. 1999;341:793-800.
159. Oger E, Bressollette L, Nonent M, Lacut K, Guias B, Couturaud F, et al. High prevalence of asymptomatic deep vein thrombosis on admission in a medical unit among elderly patients. Thromb Haemost. 2002;88:592-7.
160. Wait M, Hunt JL, Purdue GF. Duplex scanning of central vascular access sites in burn patients. Ann Surg. 1990;211:499-503.
161. Wahl WL, Brandt MM, Ahrns KS, Zajkowski PJ, Proctor MC, Wakefield TW, et al. Venous thrombosis incidence in burn patients: preliminary results of a prospective study. J Burn Care Rehabil. 2002;23:97-102.
162. Wibbenmeyer LA, Hoballah JJ, Amelon MJ, Chang PX, Loret De Mola RM, Lewis RD, 2nd, et al. The prevalence of venous thromboembolism of the lower extremity among thermally injured patients determined by duplex sonography. J Trauma. 2003;55:1162-7.
163. Demers C, Marcoux S, Ginsberg JS, Laroche F, Cloutier R, Poulin J. Incidence of venographically proved deep vein thrombosis after knee arthroscopy. Arch Intern Med. 1998;158:47-50.
164. Williams JS, Jr., Hulstyn MJ, Fadale PD, Lindy PB, Ehrlich MG, Cronan J, et al. Incidence of deep vein thrombosis after arthroscopic knee surgery: a prospective study. Arthroscopy. 1995;11:701-5.
165. Jaureguito JW, Greenwald AE, Wilcox JF, Paulos LE, Rosenberg TD. The incidence of deep venous thrombosis after arthroscopic knee surgery. Am J Sports Med. 1999;27:707-10.
166. Delis KT, Hunt N, Strachan RK, Nicolaides AN. Incidence, natural history and risk factors of deep vein thrombosis in elective knee arthroscopy. Thromb Haemost. 2001;86:817-21.
167. Wirth T, Schneider B, Misselwitz F, Lomb M, Tuylu H, Egbring R, et al. Prevention of venous thromboembolism after knee arthroscopy with low-molecular weight heparin (reviparin): Results of a randomized controlled trial. Arthroscopy. 2001;17:393-9.
168. Michot M, Conen D, Holtz D, Erni D, Zumstein MD, Ruflin GB, et al. Prevention of deep-vein thrombosis in ambulatory arthroscopic knee surgery: A randomized trial of prophylaxis with low—molecular weight heparin. Arthroscopy. 2002;18:257-63.
169. McKenna R, Bachmann F, Kaushal SP, Galante JO. Thromboembolic disease in patients undergoing total knee replacement. J Bone Joint Surg Am. 1976;58:928-32.
170. Collins R, Baigent C, Sandercock P, Peto R. Antiplatelet therapy for thromboprophylaxis: the need for careful consideration of the evidence from randomised trials. Antiplatelet Trialists' Collaboration. BMJ. 1994;309:1215-7.
171. Lassen MR, Borris LC. Thromboprophylaxis in hip fracture patients. In: Comerota AJ, Bergqvist D, Nicolaides AN, Scurr JH, eds. Prevention of venous thromboemboloism. London: Med-Orion; 1994:281-95.
172. Seagroatt V, Tan HS, Goldacre M, Bulstrode C, Nugent I, Gill L. Elective total hip replacement: incidence, emergency readmission rate, and postoperative mortality. Bmj. 1991;303:1431-5.
173. Sheppeard H, Henson J, Ward DJ, O'Connor BT. A clinico-pathological study of fatal pulmonary embolism in a specialist orthopaedic hospital. Arch Orthop Trauma Surg. 1981;99:65-71.
174. Warwick D, Williams MH, Bannister GC. Death and thromboembolic disease after total

hip replacement. A series of 1162 cases with no routine chemical prophylaxis. J Bone Joint Surg Br. 1995;77:6-10.
175. Wroblewski BM, Siney PD, White R. Fatal pulmonary embolism after total hip arthroplasty. Seasonal variation. Clin Orthop Relat Res. 1992:222-4.
176. Fender D, Harper WM, Thompson JR, Gregg PJ. Mortality and fatal pulmonary embolism after primary total hip replacement. Results from a regional hip register. J Bone Joint Surg Br. 1997;79:896-9.
177. Sigel B, Felix WR, Justin JR, al. e. Prospective identification of the pulmonary embolism prone patient employing multivariable risk factor analysis. In: Nicolaides AN, ed. Thromboembolism, aetiology, advances in prevention and management. Lancaster: Medical and technical publishing Co Ltd; 1975:181-91.
178. Nicolaides AN, Irving D. Clinical factors and the risk of deep venous thrombosis. In: Nicolaides AN, ed. Thromboembolism, aetiology, advances in prevention and management. Lancaster: Medical and technical publishing Co Ltd.; 1975:193-204.
179. Salzman EW, Hirsh J. Prevention of venous thromboembolism. In: Colman RW, Hirsh J, Marder VJ, Salzman EW, eds. Hemostasis and thrombosis, basic principles and clinical practice. New York: Lippincott; 1982:986.
180. Huber O, Bounameaux H, Borst F, Rohner A. Postoperative pulmonary embolism after hospital discharge. An underestimated risk. Arch Surg. 1992;127:310-3.
181. Arcelus JI, Caprini JA, Traverso CI. Venous thromboembolism after hospital discharge. Semin Thromb Hemost. 1993;19 Suppl 1:142-6.
182. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thromb Haemost. 2003;90:446-55.
183. Saarinen J, Sisto T, Laurikka J, Salenius JP, Tarkka M. The incidence of postoperative deep vein thrombosis in vascular procedures. FINNVASC Study Group. Vasa. 1995;24:126-9.
184. Bounameaux H, Didier D, Polat O, Desmarais S, de Moerloose P, Huber O. Antithrombotic prophylaxis in patients undergoing laparoscopic cholecystectomy. Thromb Res. 1997;86:271-3.
185. Wazz G, Branicki F, Taji H, Chishty I. Influence of pneumoperitoneum on the deep venous system during laparoscopy. JSLS. 2000;4:291-5.
186. Caprini JA, Arcelus JI, Laubach M, Size G, Hoffman KN, Coats RW, 2nd, et al. Postoperative hypercoagulability and deep-vein thrombosis after laparoscopic cholecystectomy. Surg Endosc. 1995;9:304-9.
187. Baca I, Schneider B, Kohler T, Misselwitz F, Zehle A, Muhe F. Prevention of thromboembolism in minimal invasive interventions and brief inpatient treatment. Results of a multicenter, prospective, randomized, controlled study with a low molecular weight heparin. Chirurg. 1997;68:1275-80.
188. Healey MG, Maher PJ, Hill DJ, Meagher SE, Tregaskis-Lye LE. The risk of venous thrombosis following gynaecological laparoscopic surgery. Med J Aust. 1998;168:524.
189. Lord RV, Ling JJ, Hugh TB, Coleman MJ, Doust BD, Nivison-Smith I. Incidence of deep vein thrombosis after laparoscopic vs minilaparotomy cholecystectomy. Arch Surg. 1998;133:967-73.
190. Mall JW, Schwenk W, Rodiger O, Zippel K, Pollmann C, Muller JM. Blinded prospective study of the incidence of deep venous thrombosis following conventional or laparoscopic colorectal resection. Br J Surg. 2001;88:99-100.

191. Patel MI, Hardman DT, Nicholls D, Fisher CM, Appleberg M. The incidence of deep venous thrombosis after laparoscopic cholecystectomy. Med J Aust. 1996;164:652-4, 56.
192. Bradbury AW, Chan YC, Darzi A, Stansby G. Thromboembolism prophylaxis during laparoscopic cholecystectomy. Br J Surg. 1997;84:962-4.
193. Blake AM, Toker SI, Dunn E. Deep venous thrombosis prophylaxis is not indicated for laparoscopic cholecystectomy. JSLS. 2001;5:215-9.
194. Filtenborg Tvedskov T, Rasmussen MS, Wille-Jorgensen P. Survey of the use of thromboprophylaxis in laparoscopic surgery in Denmark. Br J Surg. 2001;88:1413-6.
195. Catheline JM, Turner R, Gaillard JL, Rizk N, Champault G. Thromboembolism in laparoscopic surgery: risk factors and preventive measures. Surg Laparosc Endosc Percutan Tech. 1999;9:135-9.
196. Chamberlain G. Confidential inquiry into gynaecological laparoscopy. Br Med J. 1978;2:563.
197. Hjelmqvist B. Complications of laparoscopic cholecystectomy as recorded in the Swedish laparoscopy registry. Eur J Surg Suppl. 2000:18-21.
198. Scott TR, Zucker KA, Bailey RW. Laparoscopic cholecystectomy: a review of 12,397 patients. Surg Laparosc Endosc. 1992;2:191-8.
199. Lindberg F, Bergqvist D, Rasmussen I. Incidence of thromboembolic complications after laparoscopic cholecystectomy: review of the literature. Surg Laparosc Endosc. 1997;7:324-31.
200. Blaszyk H, Wollan PC, Witkiewicz AK, Bjornsson J. Death from pulmonary thromboembolism in severe obesity: lack of association with established genetic and clinical risk factors. Virchows Arch. 1999;434:529-32.
201. Blaszyk H, Bjornsson J. Factor V leiden and morbid obesity in fatal postoperative pulmonary embolism. Arch Surg. 2000;135:1410-3.
202. Maggard MA, Shugarman LR, Suttorp M, Maglione M, Sugerman HJ, Livingston EH, et al. Meta-analysis: surgical treatment of obesity. Ann Intern Med. 2005;142:547-59.
203. Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? J R Soc Med. 1989;82:203-5.
204. Kakkar VV, Corrigan TP, Fossard DP, Sutherland I, Thirwell J. Prevention of Fatal Postoperative pulmonary embolism by low doses of heparin. Reappraisal of results of international multicentre trial. Lancet. 1977;1:567-9.
205. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. An international multicentre trial. Lancet. 1975;2:45-51.
206. Pezzuoli G, Neri Serneri GG, Settembrini P, Coggi G, Olivari N, Buzzetti G, et al. Prophylaxis of fatal pulmonary embolism in general surgery using low-molecular weight heparin Cy 216: a multicentre, double-blind, randomized, controlled, clinical trial versus placebo (STEP). STEP-Study Group. Int Surg. 1989;74:205-10.
207. Marassi A, Balzano G, Mari G, D'Angelo SV, Della Valle P, Di Carlo V, et al. Prevention of postoperative deep vein thrombosis in cancer patients. A randomized trial with low molecular weight heparin (CY 216). Int Surg. 1993;78:166-70.
208. Bergqvist D, Flordal PA, Friberg B, Frisell J, Hedberg M, Ljungstrom KG, et al. Thromboprophylaxis with a low molecular weight heparin (tinzaparin) in emergency abdominal surgery. A double-blind multicenter trial. Vasa. 1996;25:156-60.
209. Kakkar VV, Boeckl O, Boneu B, Bordenave L, Brehm OA, Brucke P, et al. Efficacy and safety of a low-molecular-weight heparin and standard unfractionated heparin for

prophylaxis of postoperative venous thromboembolism: European multicenter trial. World J Surg. 1997;21:2-8.
210. ENOXACAN. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. ENOXACAN Study Group. Br J Surg. 1997;84:1099-103.
211. Creperio G, Marabini M, Ciocia G, Bergonzi M, Fincato M. Evaluation of the effectiveness and safety of Fragmin (Kabi 2165) versus calcium heparin in the prevention of deep venous thrombosis in general surgery. Minerva Chir. 1990;45:1101-6.
212. Garcea D, Martuzzi F, Santelmo N, Savoia M, Casertano MG, Furno A, et al. Post-surgical deep vein thrombosis prevention: evaluation of the risk/benefit ratio of fractionated and unfractionated heparin. Curr Med Res Opin. 1992;12:572-83.
213. Gazzaniga GM, Angelini G, Pastorino G, Santoro E, Lucchini M, Dal Pra ML. Enoxaparin in the prevention of deep venous thrombosis after major surgery: multicentric study. The Italian Study Group. Int Surg. 1993;78:271-5.
214. Haas S. Low molecular weight heparins in the prevention of venous thromboembolism in nonsurgical patients. Semin Thromb Hemost. 1999;25 Suppl 3:101-5.
215. Hartl P, Brucke P, Dienstl E, Vinazzer H. Prophylaxis of thromboembolism in general surgery: comparison between standard heparin and Fragmin. Thromb Res. 1990;57:577-84.
216. Hoffmann R, Largiader F. Perioperative prevention of thromboembolism with standard heparin and low molecular weight heparin, evaluation of postoperative hemorrhage. A double-blind, prospective, randomized and mono-center study. Langenbecks Arch Chir. 1992;377:258-61.
217. Kakkar VV, Cohen AT, Edmonson RA, Phillips MJ, Cooper DJ, Das SK, et al. Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. The Thromboprophylaxis Collaborative Group. Lancet. 1993;341:259-65.
218. Koppenhagen K, Troster E, Matthes M, Haring R. Prevention of thrombosis with low molecular weight heparin as the only substance and/or with DHE: results of clinical studies. Langenbecks Arch Chir Suppl II Verh Dtsch Ges Chir. 1990:1163-6.
219. Koppenhagen K, Adolf J, Matthes M, Troster E, Roder JD, Hass S, et al. Low molecular weight heparin and prevention of postoperative thrombosis in abdominal surgery. Thromb Haemost. 1992;67:627-30.
220. McLeod RS, Geerts WH, Sniderman KW, Greenwood C, Gregoire RC, Taylor BM, et al. Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the canadian colorectal DVT prophylaxis trial: a randomized, double-blind trial. Ann Surg. 2001;233:438-44.
221. Moreno Gonzalez E, Fontcuberta J, de la Llama F. Prophylaxis of thromboembolic disease with RO-11 (ROVI), during abdominal surgery. EMRO1 (Grupo Fstudio Multicintrico RO-11). Hepatogastroenterology. 1996;43:744-7.
222. Nurmohamed MT, Verhaeghe R, Haas S, Iriarte JA, Vogel G, van Rij AM, et al. A comparative trial of a low molecular weight heparin (enoxaparin) versus standard heparin for the prophylaxis of postoperative deep vein thrombosis in general surgery. Am J Surg. 1995;169:567-71.
223. Wolf H, Encke A, Haas S, Welzel D. Comparison of the efficacy and safety of Sandoz low

molecular weight heparin and unfractionated heparin: interim analysis of a multicenter trial. Semin Thromb Hemost. 1991;17:343-6.
224. Liezorovicz A, Picolet H, Peyrieux JC, Boissel JP. Prevention of perioperative deep vein thrombosis in general surgery: a multicentre double blind study comparing two doses of Logiparin and standard heparin. H.B.P.M. Research Group. Br J Surg. 1991;78:412-6.
225. Bounameaux H, Huber O, Khabiri E, Schneider PA, Didier D, Rohner A. Unexpectedly high rate of phlebographic deep venous thrombosis following elective general abdominal surgery among patients given prophylaxis with low-molecular-weight heparin. Arch Surg. 1993;128:326-8.
226. Bergqvist D, Burmark US, Flordal PA, Frisell J, Hallbook T, Hedberg M, et al. Low molecular weight heparin started before surgery as prophylaxis against deep vein thrombosis: 2500 versus 5000 XaI units in 2070 patients. Br J Surg. 1995;82:496-501.
227. Bjerkeset O, Larsen S, Reiertsen O. Evaluation of enoxaparin given before and after operation to prevent venous thromboembolism during digestive surgery: play-the-winner designed study. World J Surg. 1997;21:584-8.
228. Egger B, Schmid SW, Naef M, Wildi S, Buchler MW. Efficacy and safety of weight-adapted nadroparin calcium vs. heparin sodium in prevention of clinically evident thromboembolic complications in 1,190 general surgical patients. Dig Surg. 2000;17:602-09.
229. Lausen I, Jensen R, Jorgensen LN, Rasmussen MS, Lyng KM, Andersen M, et al. Incidence and prevention of deep venous thrombosis occurring late after general surgery: randomised controlled study of prolonged thromboprophylaxis. Eur J Surg. 1998;164:657-63.
230. Breddin HK. Low molecular weight heparins in the prevention of deep-vein thrombosis in general surgery. Semin Thromb Hemost. 1999;25 Suppl 3:83-9.
231. Jorgensen LN, Wille-Jorgensen P, Hauch O. Prophylaxis of postoperative thromboembolism with low molecular weight heparins. Br J Surg. 1993;80:689-704.
232. Koch A, Ziegler S, Breitschwerdt H, Victor N. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis: meta-analysis based on original patient data. Thromb Res. 2001;102:295-309.
233. Koch A, Bouges S, Ziegler S, Dinkel H, Daures JP, Victor N. Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis after major surgical intervention: update of previous meta-analyses. Br J Surg. 1997;84:750-9.
234. Leizorovicz A, Haugh MC, Chapuis FR, Samama MM, Boissel JP. Low molecular weight heparin in prevention of perioperative thrombosis. Br Med J. 1992;305:913-20.
235. Mismetti P, Laporte S, Darmon JY, Buchmuller A, Decousus H. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. Br J Surg. 2001;88:913-30.
236. Nurmohamed MT, Rosendaal FR, Buller HR, Dekker E, Hommes DW, Vandenbroucke JP, et al. Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. Lancet. 1992;340:152-6.
237. Palmer AJ, Schramm W, Kirchhof B, Bergemann R. Low molecular weight heparin and unfractionated heparin for prevention of thrombo-embolism in general surgery: a meta-analysis of randomised clinical trials. Haemostasis. 1997;27:65-74.
238. Wille-Jorgensen P, Rasmussen MS, Andersen BR, Borly L. Heparins and mechanical methods for thromboprophylaxis in colorectal surgery. Cochrane Database Syst Rev.

2003:CD001217.
239. Warkentin TE, Roberts RS, Hirsh J, Kelton JG. An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopedic patients. Arch Intern Med. 2003;163:2518-24.
240. Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med. 1995;332:1330-5.
241. Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. Br J Surg. 2005;92:1212-20.
242. Bergqvist D. Dextran. In: Verstraete M, Fuster V, Topol EJ, eds. Cardiovascular Thrombosis. Philadelphia.: Lippincott-Raven; 1998:235-50.
243. Aberg M, Bergentz SE, Hedner U. The effect of dextran on the lysability of ex vivo thrombi. Ann Surg. 1975;181:342-5.
244. Tangen O, Wik KO, I.A.M. A, Arfors K-E, Hint HC. Effects of dextran on the structure and plasmin-induced lysis of human fibrin. Thromb Res. 1972;1:487-92.
245. Allan A, Williams JT, Bolton JP, Le Quesne LP. The use of graduated compression stockings in the prevention of postoperative deep vein thrombosis. Br J Surg. 1983;70:172-4.
246. Borow M, Goldson H. Postoperative venous thrombosis. Evaluation of five methods of treatment. Am J Surg. 1981;141:245-51.
247. Holford CP. Graded compression for preventing deep venous thrombosis. Br Med J. 1976;2:969-70.
248. Scurr JH, Ibrahim SZ, Faber RG, Le Quesne LP. The efficacy of graduated compression stockings in the prevention of deep vein thrombosis. Br J Surg. 1977;64:371-3.
249. Tsapogas MJ, Goussous H, Peabody RA, Karmody AM, Eckert C. Postoperative venous thrombosis and the effectiveness of prophylactic measures. Arch Surg. 1971;103:561-7.
250. Turner GM, Cole SE, Brooks JH. The efficacy of graduated compression stockings in the prevention of deep vein thrombosis after major gynaecological surgery. Br J Obstet Gynaecol. 1984;91:588-91.
251. Inada K, Shirai N, Hayashi M, Matsumoto K, Hirose M. Postoperative deep venous thrombosis in Japan. Incidence and prophylaxis. Am J Surg. 1983;145:775-9.
252. Wells PS, Lensing AW, Hirsh J. Graduated compression stockings in the prevention of postoperative venous thromboembolism. A meta-analysis. Arch Intern Med. 1994;154:67-72.
253. Agu O, Hamilton G, Baker D. Graduated compression stockings in the prevention of venous thromboembolism. Br J Surg. 1999;86:992-1004.
254. Amaragiri SV, Lees TA. Elastic compression stockings for prevention of deep vein thrombosis. Cochrane Database Syst Rev. 2000:CD001484.
255. Butson AR. Intermittent pneumatic calf compression for prevention of deep venous thrombosis in general abdominal surgery. Am J Surg. 1981;142:525-7.
256. Clark WB, MacGregor AB, Prescott RJ, Ruckley CV. Pneumatic compression of the calf and postoperative deep-vein thrombosis. Lancet. 1974;2:5-7.
257. Clarke-Pearson DL, Synan IS, Hinshaw WM, Coleman RE, Creasman WT. Prevention of postoperative venous thromboembolism by external pneumatic calf compression in patients with gynecologic malignancy. Obstet Gynecol. 1984;63:92-8.

258. Hills NH, Pflug JJ, Jeyasingh K, Boardman L, Calnan JS. Prevention of deep vein thrombosis by intermittent pneumatic compression of calf. Br Med J. 1972;1:131-5.
259. Roberts VC, Cotton LT. Prevention of postoperative deep vein thrombosis in patients with malignant disease. Br Med J. 1974;1:358-60.
260. Sabri S, Roberts VC, Cotton LT. Prevention of early postoperative deep vein thrombosis by intermittent compression of the leg during surgery. Br Med J. 1971;4:394-6.
261. Turpie AG, Delmore T, Hirsh J, Hull R, Genton E, Hiscoe C, et al. Prevention of venous thrombosis by intermittent sequential calf compression in patients with intracranial disease. Thromb Res. 1979;15:611-6.
262. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet. 2000;355:1295-302.
263. Borow M, Goldson HJ. Prevention of postoperative deep venous thrombosis and pulmonary emboli with combined modalities. Am Surg. 1983;49:599-605.
264. Moser G, Froidevaux A. [Prophylaxis of Post-operative deep venous thrombosis using small sub-cutaneous heparin doses, associated or not with compressive stockings: comparative study and results (author's transl)]. Schweiz Rundsch Med Prax. 1976;65:1015-20.
265. Rasmussen A, Hansen PT, Lindholt J, Poulsen TD, Toftdahl DB, Gram J, et al. Venous thrombosis after abdominal surgery. A comparison between subcutaneous heparin and antithrombotic stockings, or both. J Med. 1988;19:193-201.
266. Torngren S. Low dose heparin and compression stockings in the prevention of postoperative deep venous thrombosis. Br J Surg. 1980;67:482-4.
267. Wille-Jorgensen P, Thorup J, Fischer A, Holst-Christensen J, Flamsholt R. Heparin with and without graded compression stockings in the prevention of thromboembolic complications of major abdominal surgery: a randomized trial. Br J Surg. 1985; 72:579-81.
268. Wille-Jorgensen P, Hauch O, Dimo B, Christensen SW, Jensen R, Hansen B. Prophylaxis of deep venous thrombosis after acute abdominal operation. Surg Gynecol Obstet. 1991;172:44-8.
269. Bergqvist D, Lindblad B. The thromboprophylactic effect of graded elastic compression stockings in combination with dextran 70. Arch Surg. 1984;119:1329-31.
270. Scurr JH, Coleridge-Smith PD, Hasty JH. Regimen for improved effectiveness of intermittent pneumatic compression in deep venous thrombosis prophylaxis. Surgery. 1987;102:816-20.
271. Lacut K, Bressollette L, Le Gal G, Etienne E, De Tinteniac A, Renault A, et al. Prevention of venous thrombosis in patients with acute intracerebral hemorrhage. Neurology. 2005;65:865-9.
272. Kakkar VV, Stamatakis JD, Bentley PG, Lawrence D, de Haas HA, Ward VP. Prophylaxis for postoperative deep-vein thrombosis. Synergistic effect of heparin and dihydroergotamine. JAMA. 1979;241:39-42.
273. Hohl MK, Luscher KP, Annaheim M, Fridrich R, Gruber UF. Dihydroergotamine and heparin or heparin alone for the prevention of postoperative thromboembolism in gynecology. Arch Gynecol. 1980;230:15-9.
274. Brucke P, Dienstl E, Vinazzer H, Simma W. Prophylaxis of postoperative thromboembolism: low dose heparin versus heparin plus dihydroergotamine. Thromb Res. 1983;29:377-82.

275. Veth G, Meuwissen OJ, van Houwelingen HC, Sixma JJ. Prevention of postoperative deep vein thrombosis by a combination of subcutaneous heparin with subcutaneous dihydroergotamine or oral sulphinpyrazone. Thromb Haemost. 1985;54:570-3.
276. Gent M, Roberts RS. A meta-analysis of the studies of dihydroergotamine plus heparin in the prophylaxis of deep vein thrombosis. Chest. 1986;89:396S-400S.
277. Sasahara AA, Koppenhagen K, Haring R, Welzel D, Wolf H. Low molecular weight heparin plus dihydroergotamine for prophylaxis of postoperative deep vein thrombosis. Br J Surg. 1986;73:697-700.
278. Pedersen B, Christiansen J. Thromboembolic prophylaxis with dihydroergotamine-heparin in abdominal surgery. A controlled, randomized study. Am J Surg. 1983;145:788-90.
279. Committee. TMt. Dihydroergotamine-heparin prophylaxis of postoperative deep vein thrombosis: a multicenter trial. JAMA. 1984;251:2960-6.
280. Ramos R, Salem BI, De Pawlikowski MP, Coordes C, Eisenberg S, Leidenfrost R. The efficacy of pneumatic compression stockings in the prevention of pulmonary embolism after cardiac surgery. Chest. 1996;109:82-5.
281. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Arch Intern Med. 2002;162:1245-8.
282. Heit JA, Melton LJ, 3rd, Lohse CM, Petterson TM, Silverstein MD, Mohr DN, et al. Incidence of venous thromboembolism in hospitalized patients vs community residents. Mayo Clin Proc. 2001;76:1102-10.
283. Bergqvist D. [Prolonged postoperative thromboprophylaxis—current state of knowledge]. Lakartidningen. 2002;99:1461-3.
284. Rasmussen MS. Preventing thromboembolic complications in cancer patients after surgery: a role for prolonged thromboprophylaxis. Cancer Treat Rev. 2002;28:141-4.
285. Wu EC, Barba CA. Current practices in the prophylaxis of venous thromboembolism in bariatric surgery. Obes Surg. 2000;10:7-13.
286. Scholten DJ, Hoedema RM, Scholten SE. A comparison of two different prophylactic dose regimens of low molecular weight heparin in bariatric surgery. Obes Surg. 2002;12:19-24.
287. Rossignol G, Leandri P, Gautier JR, Quintens H, Gabay-Torbiero L, Tap G. Radical retropubic prostatectomy: complications and quality of life (429 cases, 1983-1989). Eur Urol. 1991;19:186-91.
288. Heinzer H, Hammerer P, Graefen M, Huland H. Thromboembolic complication rate after radical retropubic prostatectomy. Impact of routine ultrasonography for the detection of pelvic lymphoceles and hematomas. Eur Urol. 1998;33:86-90.
289. Sebeseri O, Kummer H, Zingg E. Controlled prevention of post-operative thrombosis in urological diseases with depot heparin. Eur Urol. 1975;1:229-30.
290. Sieber PR, Rommel FM, Agusta VE, Breslin JA, Harpster LE, Huffnagle HW, et al. Is heparin contraindicated in pelvic lymphadenectomy and radical prostatectomy? J Urol. 1997;158:869-71.
291. Greer IA. Epidemiology, risk factors and prophylaxis of venous thrombo-embolism in obstetrics and gynaecology. Baillieres Clin Obstet Gynaecol. 1997;11:403-30.
292. Report of the National Confidential Enquiry into perioperative Deaths. 1991/92. In: HMSO, ed. London; 1993.

293. Crandon AJ, Peel KR, Anderson JA, Thompson V, McNicol GP. Postoperative deep vein thrombosis: identifying high-risk patients. Br Med J. 1980;281:343-4.
294. Clarke-Pearson DL, DeLong ER, Synan IS, Coleman RE, Creasman WT. Variables associated with postoperative deep venous thrombosis: a prospective study of 411 gynecology patients and creation of a prognostic model. Obstet Gynecol. 1987;69:146-50.
295. Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Oral contraceptives, hormone replacement therapy and thrombosis. Thromb Haemost. 2001;86:112-23.
296. Dawe F, Meltzer H. Contraception and Sexual Health 2002. In: A report on research using the ONS Omnibus Survey produced by the Office of National statistics on behalf of the Department of Health. London; 2003.
297. Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. Lancet. 1995;346:1589-93.
298. Vessey MP, Doll R, Fairbairn AS, Glober G. Postoperative thromboembolism and the use of oral contraceptives. Br Med J. 1970;3:123-6.
299. Conard J, Plu-Bureau G, Bahi N, Horellou MH, Pelissier C, Thalabard JC. Progestogen-only contraception in women at high risk of venous thromboembolism. Contraception. 2004;70:437-41.
300. Grady D, Wenger NK, Herrington D, Khan S, Furberg C, Hunninghake D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease. The Heart and Estrogen/progestin Replacement Study. Ann Intern Med. 2000;132:689-96.
301. Greer IA, Walker ID. Hormone replacement therapy and venous thromboembolism. In: Royal College of Obstetricians and Gynaecologists, guideline no 19. London; 2004.
302. Scarabin PY, Oger E, Plu-Bureau G. Differential association of oral and transdermal oestrogen-replacement therapy with venous thromboembolism risk. Lancet. 2003;362:428-32.
303. Hohl MK, Luscher KP, Tichy J, Stiner M, Fridrich R, Gruber UF, et al. Prevention of postoperative thromboembolism by dextran 70 or low-dose heparin. Obstet Gynecol. 1980;55:497-500.
304. Borstad E, Urdal K, Handeland G, Abildgaard U. Comparison of low molecular weight heparin vs. unfractionated heparin in gynecological surgery. Acta Obstet Gynecol Scand. 1988;67:99-103.
305. Maxwell GL, Synan I, Dodge R, Carroll B, Clarke-Pearson DL. Pneumatic compression versus low molecular weight heparin in gynecologic oncology surgery: a randomized trial. Obstet Gynecol. 2001;98:989-95.
306. Clarke-Pearson DL, Synan IS, Dodge R, Soper JT, Berchuck A, Coleman RE. A randomized trial of low-dose heparin and intermittent pneumatic calf compression for the prevention of deep venous thrombosis after gynecologic oncology surgery. Am J Obstet Gynecol. 1993;168:1146-53.
307. Baykal C, Al A, Demirtas E, Ayhan A. Comparison of enoxaparin and standard heparin in gynaecologic oncologic surgery: a randomised prospective double-blind clinical study. Eur J Gynaecol Oncol. 2001;22:127-30.
308. Fricker JP, Vergnes Y, Schach R, Heitz A, Eber M, Grunebaum L, et al. Low dose heparin versus low molecular weight heparin (Kabi 2165, Fragmin) in the prophylaxis of thromboembolic complications of abdominal oncological surgery. Eur J Clin Invest. 1988;18:561-7.

309. Heilmann L, Kruck M, Schindler AE. Prevention of thrombosis in gynecology: double-blind comparison of low molecular weight heparin and unfractionated heparin. Geburtshilfe Frauenheilkd. 1989;49:803-7.
310. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. Why mothers die 2000-2002. In: 6th report, RCOG Press. London; 2004.
311. Bonnar J. Venous Thromboembolism and Pregnancy. In: Dalen JE, ed. Venous Thromboembolism. New York: Marcel Dekker; 2003:217-33.
312. Gates S, Brocklehurst P, Davis LJ. Prophylaxis for venous thromboembolic disease in pregnancy and the early postnatal period. Cochrane Database Syst Rev. 2002:CD001689.
313. Sanson BJ, Lensing AW, Prins MH, Ginsberg JS, Barkagan ZS, Lavenne-Pardonge E, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. Thromb Haemost. 1999;81:668-72.
314. Lepercq J, Conard J, Borel-Derlon A, Darmon JY, Boudignat O, Francoual C, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. Br J Obstet Gynaecol. 2001;108:1134-40.
315. Bates SM, Greer IA, Hirsh J, Ginsberg JS. Use of antithrombotic agents during pregnancy: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:627S-44S.
316. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005;106:401-7.
317. Ensom MH, Stephenson MD. Low-molecular-weight heparins in pregnancy. Pharmacotherapy. 1999;19:1013-25.
318. Nelson-Piercy C, Letsky EA, de Swiet M. Low-molecular-weight heparin for obstetric thromboprophylaxis: experience of sixty-nine pregnancies in sixty-one women at high risk. Am J Obstet Gynecol. 1997;176:1062-8.
319. Pettila V, Leinonen P, Markkola A, Hiilesmaa V, Kaaja R. Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. Thromb Haemost. 2002;87:182-6.
320. Brill-Edwards P, Ginsberg JS, Gent M, Hirsh J, Burrows R, Kearon C, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. Recurrence of Clot in This Pregnancy Study Group. N Engl J Med. 2000;343:1439-44.
321. Pabinger I, Grafenhofer H, Kyrle PA, Quehenberger P, Mannhalter C, Lechner K, et al. Temporary increase in the risk for recurrence during pregnancy in women with a history of venous thromboembolism. Blood. 2002;100:1060-2.
322. Smith MP, Norris LA, Steer PJ, Savidge GF, Bonnar J. Tinzaparin sodium for thrombosis treatment and prevention during pregnancy. Am J Obstet Gynecol. 2004;190:495-501.
323. Norris LA, Bonnar J, Smith MP, Steer PJ, Savidge G. Low molecular weight heparin (tinzaparin) therapy for moderate risk thromboprophylaxis during pregnancy. A pharmacokinetic study. Thromb Haemost. 2004;92:791-6.
324. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). Br Med J. 1997;314:253-7.
325. Empson M, Lassere M, Craig J, Scott J. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. Cochrane Database Syst Rev. 2005:CD002859.

326. Checketts MR, Wildsmith JA. Epidural haematoma following anticoagulant treatment in a patient with an indwelling epidural catheter. Anaesthesia. 1999;54:87-8.
327. Horlocker TT, Wedel DJ. Neuraxial block and low-molecular-weight heparin: balancing perioperative analgesia and thromboprophylaxis. Reg Anesth Pain Med. 1998;23:164-77.
328. McKenna R, Cole ER, Vasan U. Is warfarin sodium contraindicated in the lactating mother? J Pediatr. 1983;103:325-7.
329. O'Reilly R. Anticoagulant, antithrombotic and thrombolytic drugs. In: Gillman AGea, ed. The pharmacologic basis of therapeutics. 6 ed. New York.: Macmillan; 1980:1347.
330. Hirsh J. Prevention of venous thrombosis in patients undergoing major orthopaedic surgical procedures. Acta Chir Scand Suppl. 1990;556:30-5.
331. White RH, Romano PS, Zhou H, Rodrigo J, Bargar W. Incidence and time course of thromboembolic outcomes following total hip or knee arthroplasty. Arch Intern Med. 1998;158:1525-31.
332. Turner RS, Griffiths H, Heatley FW. The incidence of deep-vein thrombosis after upper tibial osteotomy. A venographic study. J Bone Joint Surg Br. 1993;75:942-4.
333. Dahl OE, Gudmundsen TE, Bjornara BT, Solheim DM. Risk of clinical pulmonary embolism after joint surgery in patients receiving low-molecular-weight heparin prophylaxis in hospital: a 10-year prospective register of 3,954 patients. Acta Orthop Scand. 2003;74:299-304.
334. Dahl OE, Gudmundsen TE, Haukeland L. Late occurring clinical deep vein thrombosis in joint-operated patients. Acta Orthop Scand. 2000;71:47-50.
335. Lie SA, Engesaeter LB, Havelin LI, Furnes O, Vollset SE. Early postoperative mortality after 67,548 total hip replacements: causes of death and thromboprophylaxis in 68 hospitals in Norway from 1987 to 1999. Acta Orthop Scand. 2002;73:392-9.
336. Lie SA, Engesaeter LB, Havelin LI, Gjessing HK, Vollset SE. Mortality after total hip replacement: 0-10-year follow-up of 39,543 patients in the Norwegian Arthroplasty Register. Acta Orthop Scand. 2000;71:19-27.
337. Beisaw NE, Comerota AJ, Groth HE, Merli GJ, Weitz HH, Zimmerman RC, et al. Dihydroergotamine/heparin in the prevention of deep-vein thrombosis after total hip replacement. A controlled, prospective, randomized multicenter trial. J Bone Joint Surg Am. 1988;70:2-10.
338. Haake DA, Berkman SA. Venous thromboembolic disease after hip surgery. Risk factors, prophylaxis, and diagnosis. Clin Orthop Relat Res. 1989:212-31.
339. Lassen MR, Borris LC, Christiansen HM, Schott P, Olsen AD, Sorensen JV, et al. Clinical trials with low molecular weight heparins in the prevention of postoperative thromboembolic complications: a meta-analysis. Semin Thromb Hemost. 1991;17 Suppl 3:284-90.
340. Freedman KB, Brookenthal KR, Fitzgerald RH, Jr., Williams S, Lonner JH. A meta-analysis of thromboembolic prophylaxis following elective total hip arthroplasty. J Bone Joint Surg Am. 2000;82-A:929-38.
341. Lotke PA, Palevsky H, Keenan AM, Meranze S, Steinberg ME, Ecker ML, et al. Aspirin and warfarin for thromboembolic disease after total joint arthroplasty. Clin Orthop Relat Res. 1996:251-8.
342. Westrich GH, Sculco TP. Prophylaxis against deep venous thrombosis after total knee arthroplasty. Pneumatic plantar compression and aspirin compared with aspirin alone. J Bone Joint Surg Am. 1996;78:826-34.

343. Fisher CG, Blachut PA, Salvian AJ, Meek RN, O'Brien PJ. Effectiveness of pneumatic leg compression devices for the prevention of thromboembolic disease in orthopaedic trauma patients: a prospective, randomized study of compression alone versus no prophylaxis. J Orthop Trauma. 1995;9:1-7.
344. Hartman JT, Pugh JL, Smith RD, Robertson WW, Jr., Yost RP, Janssen HF. Cyclic sequential compression of the lower limb in prevention of deep venous thrombosis. J Bone Joint Surg Am. 1982;64:1059-62.
345. Haas SB, Insall JN, Scuderi GR, Windsor RE, Ghelman B. Pneumatic sequential-compression boots compared with aspirin prophylaxis of deep-vein thrombosis after total knee arthroplasty. J Bone Joint Surg Am. 1990;72:27-31.
346. Bradley JG, Krugener GH, Jager HJ. The effectiveness of intermittent plantar venous compression in prevention of deep venous thrombosis after total hip arthroplasty. J Arthroplasty. 1993;8:57-61.
347. Fordyce MJ, Ling RS. A venous foot pump reduces thrombosis after total hip replacement. J Bone Joint Surg Br. 1992;74:45-9.
348. Santori FS, Vitullo A, Stopponi M, Santori N, Ghera S. Prophylaxis against deep-vein thrombosis in total hip replacement. Comparison of heparin and foot impulse pump. J Bone Joint Surg Br. 1994;76:579-83.
349. Warwick D, Harrison J, Glew D, Mitchelmore A, Peters TJ, Donovan J. Comparison of the use of a foot pump with the use of low-molecular-weight heparin for the prevention of deep-vein thrombosis after total hip replacement. A prospective, randomized trial. J Bone Joint Surg Am. 1998;80:1158-66.
350. Pitto RP, Hamer H, Heiss-Dunlop W, Kuehle J. Mechanical prophylaxis of deep-vein thrombosis after total hip replacement a randomised clinical trial. J Bone Joint Surg Br. 2004;86:639-42.
351. Blanchard J, Meuwly JY, Leyvraz PF, Miron MJ, Bounameaux H, Hoffmeyer P, et al. Prevention of deep-vein thrombosis after total knee replacement. Randomised comparison between a low-molecular-weight heparin (nadroparin) and mechanical prophylaxis with a foot-pump system. J Bone Joint Surg Br. 1999;81:654-9.
352. Warwick D, Harrison J, Whitehouse S, Mitchelmore A, Thornton M. A randomised comparison of a foot pump and low-molecular-weight heparin in the prevention of deep-vein thrombosis after total knee replacement. J Bone Joint Surg Br. 2002;84:344-50.
353. Stranks GJ, MacKenzie NA, Grover ML, Fail T. The A-V Impulse System reduces deep-vein thrombosis and swelling after hemiarthroplasty for hip fracture. J Bone Joint Surg Br. 1992;74:775-8.
354. Heit JA, Berkowitz SD, Bona R, Cabanas V, Corson JD, Elliott CG, et al. Efficacy and safety of low molecular weight heparin (ardeparin sodium) compared to warfarin for the prevention of venous thromboembolism after total knee replacement surgery: a double-blind, dose-ranging study. Ardeparin Arthroplasty Study Group. Thromb Haemost. 1997;77:32-8.
355. Hull R, Raskob G, Pineo G, Rosenbloom D, Evans W, Mallory T, et al. A comparison of subcutaneous low-molecular-weight heparin with warfarin sodium for prophylaxis against deep-vein thrombosis after hip or knee implantation. N Engl J Med. 1993;329:1370-6.
356. RD heparin compared with warfarin for prevention of venous thromboembolic disease following total hip or knee arthroplasty. RD Heparin Arthroplasty Group. J Bone Joint Surg Am. 1994;76:1174-85.

357. Fitzgerald RH, Jr., Spiro TE, Trowbridge AA, Gardiner GA, Jr., Whitsett TL, O'Connell MB, et al. Prevention of venous thromboembolic disease following primary total knee arthroplasty. A randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. J Bone Joint Surg Am. 2001;83-A:900-6.
358. Hamulyak K, Lensing AW, van der Meer J, Smid WM, van Ooy A, Hoek JA. Subcutaneous low-molecular weight heparin or oral anticoagulants for the prevention of deep-vein thrombosis in elective hip and knee replacement? Fraxiparine Oral Anticoagulant Study Group. Thromb Haemost. 1995;74:1428-31.
359. Bergqvist D, Benoni G, Bjorgell O, Fredin H, Hedlundh U, Nicolas S, et al. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. N Engl J Med. 1996;335:696-700.
360. Levine MN, Hirsh J, Gent M, Turpie AG, Leclerc J, Powers PJ, et al. Prevention of deep vein thrombosis after elective hip surgery. A randomized trial comparing low molecular weight heparin with standard unfractionated heparin. Ann Intern Med. 1991;114:545-51.
361. Colwell CW, Jr., Spiro TE, Trowbridge AA, Morris BA, Kwaan HC, Blaha JD, et al. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety. Enoxaparin Clinical Trial Group. J Bone Joint Surg Am. 1994;76:3-14.
362. Planes A, Vochelle N, Mazas F, Mansat C, Zucman J, Landais A, et al. Prevention of postoperative venous thrombosis: a randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. Thromb Haemost. 1988;60:407-10.
363. Prevention of deep vein thrombosis with low molecular-weight heparin in patients undergoing total hip replacement. A randomized trial. The German Hip Arthroplasty Trial (GHAT) Group. Arch Orthop Trauma Surg. 1992;111:110-20.
364. Eriksson BI, Kalebo P, Ekman S, Lindbratt S, Kerry R, Close P. Direct thrombin inhibition with Rec-hirudin CGP 39393 as prophylaxis of thromboembolic complications after total hip replacement. Thromb Haemost. 1994;72:227-31.
365. Eriksson BI, Wille-Jorgensen P, Kalebo P, Mouret P, Rosencher N, Bosch P, et al. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. N Engl J Med. 1997;337:1329-35.
366. Eriksson BI, Ekman S, Lindbratt S, Baur M, Bach D, Torholm C, et al. Prevention of thromboembolism with use of recombinant hirudin. Results of a double-blind, multicenter trial comparing the efficacy of desirudin (Revasc) with that of unfractionated heparin in patients having a total hip replacement. J Bone Joint Surg Am. 1997;79:326-33.
367. Francis CW, Pellegrini VD, Jr., Totterman S, Boyd AD, Jr., Marder VJ, Liebert KM, et al. Prevention of deep-vein thrombosis after total hip arthroplasty. Comparison of warfarin and dalteparin. J Bone Joint Surg Am. 1997;79:1365-72.
368. Hull RD, Pineo GF, Francis C, Bergqvist D, Fellenius C, Soderberg K, et al. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs warfarin in hip arthroplasty patients: a double-blind, randomized comparison. The North American Fragmin Trial Investigators. Arch Intern Med. 2000;160:2199-207.
369. Hull RD, Pineo GF, Stein PD, Mah AF, MacIsaac SM, Dahl OE, et al. Timing of initial administration of low-molecular-weight heparin prophylaxis against deep vein thrombosis

in patients following elective hip arthroplasty: a systematic review. Arch Intern Med. 2001;161:1952-60.
370. Mismetti P, Laporte S, Zufferey P, Epinat M, Decousus H, Cucherat M. Prevention of venous thromboembolism in orthopedic surgery with vitamin K antagonists: a meta-analysis. J Thromb Haemost. 2004;2:1058-70.
371. Samama CM, Vray M, Barre J, Fiessinger JN, Rosencher N, Lecompte T, et al. Extended venous thromboembolism prophylaxis after total hip replacement: a comparison of low-molecular-weight heparin with oral anticoagulant. Arch Intern Med. 2002;162:2191-6.
372. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BrMedJ. 2004;329:15-9.
373. Budnitz DS, Pollock DA, Mendelsohn AB, Weidenbach KN, McDonald AK, Annest JL. Emergency department visits for outpatient adverse drug events: demonstration for a national surveillance system. Ann Emerg Med. 2005;45:197-206.
374. Lassen MR, Bauer KA, Eriksson BI, Turpie AG. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomised double-blind comparison. Lancet. 2002;359:1715-20.
375. Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomised double-blind trial. Lancet. 2002;359:1721-6.
376. Cohen A, Quinlan D. PEP trial. Pulmonary Embolism Prevention. Lancet. 2000;356:247.
377. Barnes RW, Brand RA, Clarke W, Hartley N, Hoak JC. Efficacy of graded-compression antiembolism stockings in patients undergoing total hip arthroplasty. Clin Orthop Relat Res. 1978:61-7.
378. Silbersack Y, Taute BM, Hein W, Podhaisky H. Prevention of deep-vein thrombosis after total hip and knee replacement. Low-molecular-weight heparin in combination with intermittent pneumatic compression. J Bone Joint Surg Br. 2004;86:809-12.
379. Warwick D. Intermittent pneumatic compression prophylaxis for proximal deep venous thrombosis after total hip replacement. J Bone Joint Surg Am. 1998;80:141-2.
380. Kakkos SK, Szendro G, Griffin M, Sabetai MM, Nicolaides AN. Improved hemodynamic effectiveness and associated clinical correlations of a new intermittent pneumatic compression system in patients with chronic venous insufficiency. J Vasc Surg. 2001;34:915-22.
381. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Lassen MR, Mouret P, et al. The direct thrombin inhibitor melagatran followed by oral ximelagatran compared with enoxaparin for the prevention of venous thromboembolism after total hip or knee replacement: the EXPRESS study. J Thromb Haemost. 2003;1:2490-6.
382. Eriksson BI, Bergqvist D, Kalebo P, Dahl OE, Lindbratt S, Bylock A, et al. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. Lancet. 2002;360:1441-7.
383. Eriksson BI, Arfwidsson AC, Frison L, Eriksson UG, Bylock A, Kalebo P, et al. A dose-ranging study of the oral direct thrombin inhibitor, ximelagatran, and its subcutaneous form, melagatran, compared with dalteparin in the prophylaxis of thromboembolism after hip or knee replacement: METHRO I. MElagatran for THRombin inhibition in Orthopaedic surgery. Thromb Haemost. 2002;87:231-7.

384. Eriksson BI, Agnelli G, Cohen AT, Dahl OE, Mouret P, Rosencher N, et al. Direct thrombin inhibitor melagatran followed by oral ximelagatran in comparison with enoxaparin for prevention of venous thromboembolism after total hip or knee replacement. Thromb Haemost. 2003;89:288-96.
385. Urwin SC, Parker MJ, Griffiths R. General versus regional anaesthesia for hip fracture surgery: a meta-analysis of randomized trials. Br J Anaesth. 2000;84:450-5.
386. Parker MJ, Urwin SC, Handoll HH, Griffiths R. General versus spinal/epidural anaesthesia for surgery for hip fractures in adults. Cochrane Database Syst Rev. 2000:CD000521.
387. Williams-Russo P, Sharrock NE, Haas SB, Insall J, Windsor RE, Laskin RS, et al. Randomized trial of epidural versus general anesthesia: outcomes after primary total knee replacement. Clin Orthop Relat Res. 1996:199-208.
388. Sharrock NE, Haas SB, Hargett MJ, Urquhart B, Insall JN, Scuderi G. Effects of epidural anesthesia on the incidence of deep-vein thrombosis after total knee arthroplasty. J Bone Joint Surg Am. 1991;73:502-6.
389. Nielsen PT, Jorgensen LN, Albrecht-Beste E, Leffers AM, Rasmussen LS. Lower thrombosis risk with epidural blockade in knee arthroplasty. Acta Orthop Scand. 1990;61:29-31.
390. Matzsch T, Bergqvist D, Johansson A. An inquiry shows minimal risk of hemorrhage resulting from thrombosis prevention in regional anesthesia. Lakartidningen. 1992;89:4028-30.
391. Tryba M, Wedel DJ. Central neuraxial block and low molecular weight heparin (enoxaparine): lessons learned from different dosage regimes in two continents. Acta Anaesthesiol Scand Suppl. 1997;111:100-4.
392. Wysowski DK, Talarico L, Bacsanyi J, Botstein P. Spinal and epidural hematoma and low-molecular-weight heparin. N Engl J Med. 1998;338:1774-5.
393. Horlocker TT. Low molecular weight heparin and neuraxial anesthesia. Thromb Res. 2001;101:V141-54.
394. Strebel N, Prins M, Agnelli G, Buller HR. Preoperative or postoperative start of prophylaxis for venous thromboembolism with low-molecular-weight heparin in elective hip surgery? Arch Intern Med. 2002;162:1451-6.
395. Hooker JA, Lachiewicz PF, Kelley SS. Efficacy of prophylaxis against thromboembolism with intermittent pneumatic compression after primary and revision total hip arthroplasty. J Bone Joint Surg Am. 1999;81:690-6.
396. Woolson ST, Robinson RK, Khan NQ, Roqers BS, Maloney WJ. Deep venous thrombosis prophylaxis for knee replacement: warfarin and pneumatic compression. Am J Orthop. 1998;27:299-304.
397. Pellegrini VD, Jr., Langhans MJ, Totterman S, Marder VJ, Francis CW. Embolic complications of calf thrombosis following total hip arthroplasty. J Arthroplasty. 1993;8:449-57.
398. Trowbridge A, Boese CK, Woodruff B, Brindley HH, Sr., Lowry WE, Spiro TE. Incidence of posthospitalization proximal deep venous thrombosis after total hip arthroplasty. A pilot study. Clin Orthop Relat Res. 1994:203-8.
399. Bjorgell O, Nilsson PE, Benoni G, Bergqvist D. Symptomatic and asymptomatic deep vein thrombosis after total hip replacement. Differences in phlebographic pattern, described by a scoring of the thrombotic burden. Thromb Res. 2000;99:429-38.

400. Amstutz HC, Friscia DA, Dorey F, Carney BT. Warfarin prophylaxis to prevent mortality from pulmonary embolism after total hip replacement. J Bone Joint Surg Am. 1989;71:321-6.
401. Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Huet Y. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. Lancet. 1996;348:224-8.
402. Colwell CW, Jr., Collis DK, Paulson R, McCutchen JW, Bigler GT, Lutz S, et al. Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty. Evaluation during hospitalization and three months after discharge. J Bone Joint Surg Am. 1999;81:932-40.
403. Lieberman JR, Wollaeger J, Dorey F, Thomas BJ, Kilgus DJ, Grecula MJ, et al. The efficacy of prophylaxis with low-dose warfarin for prevention of pulmonary embolism following total hip arthroplasty. J Bone Joint Surg Am. 1997;79:319-25.
404. Hull RD, Pineo GF, Francis C, Bergqvist D, Fellenius C, Soderberg K, et al. Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients: a double-blind, randomized comparison. North American Fragmin Trial Investigators. Arch Intern Med. 2000;160:2208-15.
405. Dahl OE, Andreassen G, Aspelin T, Muller C, Mathiesen P, Nyhus S, et al. Prolonged thromboprophylaxis following hip replacement surgery—results of a double-blind, prospective, randomised, placebo-controlled study with dalteparin (Fragmin). Thromb Haemost. 1997;77:26-31.
406. Lassen MR, Borris LC, Anderson BS, Jensen HP, Skejo Bro HP, Andersen G, et al. Efficacy and safety of prolonged thromboprophylaxis with a low molecular weight heparin (dalteparin) after total hip arthroplasty—the Danish Prolonged Prophylaxis (DaPP) Study. Thromb Res. 1998;89:281-7.
407. Comp PC, Spiro TE, Friedman RJ, Whitsett TL, Johnson GJ, Gardiner GA, Jr., et al. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. Enoxaparin Clinical Trial Group. J Bone Joint Surg Am. 2001;83-A:336-45.
408. Dahl OE, Caprini JA, Colwell CW, Jr., Frostick SP, Haas S, Hull RD, et al. Fatal vascular outcomes following major orthopedic surgery. Thromb Haemost. 2005;93:860-6.
409. Prandoni P, Bruchi O, Sabbion P, Tanduo C, Scudeller A, Sardella C, et al. Prolonged thromboprophylaxis with oral anticoagulants after total hip arthroplasty: a prospective controlled randomized study. Arch Intern Med. 2002;162:1966-71.
410. Kaempffe FA, Lifeso RM, Meinking C. Intermittent pneumatic compression versus coumadin. Prevention of deep vein thrombosis in lower-extremity total joint arthroplasty. Clin Orthop Relat Res. 1991:89-97.
411. Norgren L, Toksvig-Larsen S, Magyar G, Lindstrand A, Albrechtsson U. Prevention of deep vein thrombosis in knee arthroplasty. Preliminary results from a randomized controlled study of low molecular weight heparin vs foot pump compression. Int Angiol. 1998;17:93-6.
412. Leclerc JR, Geerts WH, Desjardins L, Jobin F, Laroche F, Delorme F, et al. Prevention of deep vein thrombosis after major knee surgery—a randomized, double-blind trial comparing a low molecular weight heparin fragment (enoxaparin) to placebo. Thromb

Haemost. 1992;67:417-23.
413. Fauno P, Suomalainen O, Rehnberg V, Hansen TB, Kroner K, Soimakallio S, et al. Prophylaxis for the prevention of venous thromboembolism after total knee arthroplasty. A comparison between unfractionated and low-molecular-weight heparin. J Bone Joint Surg Am. 1994;76:1814-8.
414. Colwell CW, Jr., Spiro TE, Trowbridge AA, Stephens JW, Gardiner GA, Jr., Ritter MA. Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep venous thrombosis after elective knee arthroplasty. Enoxaparin Clinical Trial Group. Clin Orthop Relat Res. 1995:19-27.
415. Bauer KA, Eriksson BI, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. N Engl J Med. 2001;345:1305-10.
416. Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. Arch Intern Med. 2002;162:1833-40.
417. Heit JA, Colwell CW, Francis CW, Ginsberg JS, Berkowitz SD, Whipple J, et al. Comparison of the oral direct thrombin inhibitor ximelagatran with enoxaparin as prophylaxis against venous thromboembolism after total knee replacement: a phase 2 dose-finding study. Arch Intern Med. 2001;161:2215-21.
418. Francis CW, Davidson BL, Berkowitz SD, Lotke PA, Ginsberg JS, Lieberman JR, et al. Ximelagatran versus warfarin for the prevention of venous thromboembolism after total knee arthroplasty. A randomized, double-blind trial. Ann Intern Med. 2002;137:648-55.
419. Francis CW, Berkowitz SD, Comp PC, Lieberman JR, Ginsberg JS, Paiement G, et al. Comparison of ximelagatran with warfarin for the prevention of venous thromboembolism after total knee replacement. N Engl J Med. 2003;349:1703-12.
420. Colwell CW, Jr., Berkowitz SD, Lieberman JR, Comp PC, Ginsberg JS, Paiement G, et al. Oral direct thrombin inhibitor ximelagatran compared with warfarin for the prevention of venous thromboembolism after total knee arthroplasty. J Bone Joint Surg Am. 2005;87:2169-77.
421. Snook GA, Chrisman OD, Wilson TC. Thromboembolism after surgical treatment of hip fractures. Clin Orthop Relat Res. 1981:21-4.
422. Agnelli G, Cosmi B, Di Filippo P, Ranucci V, Veschi F, Longetti M, et al. A randomised, double-blind, placebo-controlled trial of dermatan sulphate for prevention of deep vein thrombosis in hip fracture. Thromb Haemost. 1992;67:203-8.
423. Todd CJ, Palmer C, Camilleri-Ferrante C, Freeman CJ, Laxton CE, Parker MJ, et al. Differences in mortality after fracture of hip. Br Med J. 1995;311:1025.
424. Barrett JA, Baron JA, Beach ML. Mortality and pulmonary embolism after fracture in the elderly. Osteoporos Int. 2003;14:889-94.
425. Monreal M, Lafoz E, Navarro A, Granero X, Caja V, Caceres E, et al. A prospective double-blind trial of a low molecular weight heparin once daily compared with conventional low-dose heparin three times daily to prevent pulmonary embolism and venous thrombosis in patients with hip fracture. J Trauma. 1989;29:873-5.
426. Thromboprophylaxis in hip fracture surgery: a pilot study comparing danaparoid, enoxaparin and dalteparin. The TIFDED Study Group. Haemostasis. 1999;29:310-7.
427. Barsotti J, Gruel Y, Rosset P, Favard L, Dabo B, Andreu J, et al. Comparative double-blind study of two dosage regimens of low-molecular weight heparin in elderly patients with a

fracture of the neck of the femur. J Orthop Trauma. 1990;4:371-5.
428. Eriksson BI, Bauer KA, Lassen MR, Turpie AG. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med. 2001;345:1298-304.
429. Handoll HH, Farrar MJ, McBirnie J, Tytherleigh-Strong G, Milne AA, Gillespie WJ. Heparin, low molecular weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. Cochrane Database Syst Rev. 2002:CD000305.
430. Borgstroem S, Greitz T, Van Der Linden W, Molin J, Rudics I. Anticoagulant Prophylaxis of Venous Thrombosis in Patients with Fractured Neck of the Femur; a Controlled Clinical Trial Using Venous Phlebography. Acta Chir Scand. 1965;129:500-8.
431. Hamilton HW, Crawford JS, Gardiner JH, Wiley AM. Venous thrombosis in patients with fracture of the upper end of the femur. A phlebographic study of the effect of prophylactic anticoagulation. J Bone Joint Surg Br. 1970;52:268-89.
432. Eriksson BI, Lassen MR. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery: a multicenter, randomized, placebo-controlled, double-blind study. Arch Intern Med. 2003;163:1337-42.
433. Roberts TS, Nelson CL, Barnes CL, Ferris EJ, Holder JC, Boone DW. The preoperative prevalence and postoperative incidence of thromboembolism in patients with hip fractures treated with dextran prophylaxis. Clin Orthop Relat Res. 1990:198-203.
434. Girasole GJ, Cuomo F, Denton JR, O'Connor D, Ernst A. Diagnosis of deep vein thrombosis in elderly hip-fracture patients by using the duplex scanning technique. Orthop Rev. 1994;23:411-6.
435. Hefley FG, Jr., Nelson CL, Puskarich-May CL. Effect of delayed admission to the hospital on the preoperative prevalence of deep-vein thrombosis associated with fractures about the hip. J Bone Joint Surg Am. 1996;78:581-3.
436. Zahn HR, Skinner JA, Porteous MJ. The preoperative prevalence of deep vein thrombosis in patients with femoral neck fractures and delayed operation. Injury. 1999;30:605-7.
437. Durica S, Raskob G, Johnson C, al. e. Incidence of deep venous thrombosis after arthroscopic knee surgery (abstr). Thromb Haemost. 1997;77(suppl):183.
438. Schippinger G, Wirnsberger GH, Obernosterer A, Babinski K. Thromboembolic complications after arthroscopic knee surgery. Incidence and risk factors in 101 patients. Acta Orthop Scand. 1998;69:144-6.
439. Geerts WH, Jay RM, Code KI, Chen E, Szalai JP, Saibil EA, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996;335:701-7.
440. Meissner MH. Deep venous thrombosis in the trauma patient. Semin Vasc Surg. 1998;11:274-82.
441. Rogers FB. Venous thromboembolism in trauma patients: a review. Surgery. 2001;130:1-12.
442. Rogers FB, Cipolle MD, Velmahos G, Rozycki G, Luchette FA. Practice management guidelines for the prevention of venous thromboembolism in trauma patients: the EAST practice management guidelines work group. J Trauma. 2002;53:142-64.
443. O'Malley KF, Ross SE. Pulmonary embolism in major trauma patients. J Trauma. 1990;30:748-50.
444. Rogers FB, Shackford SR, Wilson J, Ricci MA, Morris CS. Prophylactic vena cava filter

insertion in severely injured trauma patients: indications and preliminary results. J Trauma. 1993;35:637-41; discussion 41-2.
445. Acosta S, Nordstrom CH. Be aware of risk factors when managing brain concussion. Anticoagulant therapy is an indication for computed tomography also in patients seemingly not affected. Lakartidningen. 1998;95:5762-3.
446. Meissner MH, Chandler WL, Elliott JS. Venous thromboembolism in trauma: a local manifestation of systemic hypercoagulability? J Trauma. 2003;54:224-31.
447. Velmahos GC, Kern J, Chan LS, Oder D, Murray JA, Shekelle P. Prevention of venous thromboembolism after injury: an evidence-based report—part II: analysis of risk factors and evaluation of the role of vena caval filters. J Trauma. 2000;49:140-4.
448. Velmahos GC, Kern J, Chan LS, Oder D, Murray JA, Shekelle P. Prevention of venous thromboembolism after injury: an evidence-based report—part I: analysis of risk factors and evaluation of the role of vena caval filters. J Trauma. 2000;49:132-8.
449. Cohn S, Dolich M, Matsuura K, Namias N, Kirton O, Shatz D, et al. Digital imaging technology in trauma education: a quantum leap forward. J Trauma. 1999;47:1160-1.
450. Haentjens P. Thromboembolic prophylaxis in orthopaedic trauma patients: a comparison between a fixed dose and an individually adjusted dose of a low molecular weight heparin (nadroparin calcium). Injury. 1996;27:385-90.
451. Knudson MM, Morabito D, Paiement GD, Shackleford S. Use of low molecular weight heparin in preventing thromboembolism in trauma patients. J Trauma. 1996;41:446-59.
452. Elliott CG, Dudney TM, Egger M, Orme JF, Clemmer TP, Horn SD, et al. Calf-thigh sequential pneumatic compression compared with plantar venous pneumatic compression to prevent deep-vein thrombosis after non-lower extremity trauma. J Trauma. 1999;47:25-32.
453. Tetzlaff J, Yoon H, O'Hara J, al. e. Influence of anesthetic technique on the incidence of deep venous thrombosis after elective lumbar spine surgery (abstr). Reg Anesth Pain Med. 1994;19(suppl):28.
454. Turner JA, Ersek M, Herron L, Deyo R. Surgery for lumbar spinal stenosis. Attempted meta-analysis of the literature. Spine. 1992;17:1-8.
455. Gallus AS, Hirsh J, O'Brien SE, McBride JA, Tuttle RJ, Gent M. Prevention of venous thrombosis with small, subcutaneous doses of heparin. JAMA. 1976;235:1980-2.
456. Waring WP, Karunas RS. Acute spinal cord injuries and the incidence of clinically occurring thromboembolic disease. Paraplegia. 1991;29:8-16.
457. DeVivo MJ. Discharge disposition from model spinal cord injury care system rehabilitation programs. Arch Phys Med Rehabil. 1999;80:785-90.
458. Chen D, Apple DF, Jr., Hudson LM, Bode R. Medical complications during acute rehabilitation following spinal cord injury—current experience of the Model Systems. Arch Phys Med Rehabil. 1999;80:1397-401.
459. Green D, Lee MY, Lim AC, Chmiel JS, Vetter M, Pang T, et al. Prevention of thromboembolism after spinal cord injury using low-molecular-weight heparin. Ann Intern Med. 1990;113:571-4.
460. Prevention of venous thromboembolism in the acute treatment phase after spinal cord injury: a randomized, multicenter trial comparing low-dose heparin plus intermittent pneumatic compression with enoxaparin. J Trauma. 2003;54:1116-24; discussion 25-6.
461. Brischetto M, Brischetto M, Auer A, al. e. Venous thrombosis in burn patients (abstr). Am J Respir Crit Care Med. 1998;157:A768.

462. Harrington DT, Mozingo DW, Cancio L, Bird P, Jordan B, Goodwin CW. Thermally injured patients are at significant risk for thromboembolic complications. J Trauma. 2001;50:495-9.
463. Gnoyski JM, Keen AM, Gamelli RL, al. e. Deep venous thrombosis and the association with burns involving the lower extremities (abstr). Arch Phys Med Rehabil. 1994;75:1045.
464. Valladares JB, Hankinson J. Incidence of lower extremity deep vein thrombosis in neurosurgical patients. Neurosurgery. 1980;6:138-41.
465. Agnelli G. Prevention of venous thromboembolism after neurosurgery. Thromb Haemost. 1999;82:925-30.
466. Chan AT, Atiemo A, Diran LK, Licholai GP, McLaren Black P, Creager MA, et al. Venous thromboembolism occurs frequently in patients undergoing brain tumor surgery despite prophylaxis. J Thromb Thrombolysis. 1999;8:139-42.
467. Brandes AA, Scelzi E, Salmistraro G, Ermani M, Carollo C, Berti F, et al. Incidence of risk of thromboembolism during treatment high-grade gliomas: a prospective study. Eur J Cancer. 1997;33:1592-6.
468. Marras LC, Geerts WH, Perry JR. The risk of venous thromboembolism is increased throughout the course of malignant glioma: an evidence-based review. Cancer. 2000;89:640-6.
469. Ruff RL, Posner JB. Incidence and treatment of peripheral venous thrombosis in patients with glioma. Ann Neurol. 1983;13:334-6.
470. Walsh DC, Kakkar AK. Thromboembolism in brain tumors. Curr Opin Pulm Med. 2001;7:326-31.
471. Anderson FA, Huang W, Sullivan C, al. e. The continuing risk of venous thromboembolism following operation for glioma: findinges from Glioma Outcomes Project (abstr). Haemost Thromb. 2001;86(suppl):OC902.
472. Nurmohamed MT, van Riel AM, Henkens CM, Koopman MM, Que GT, d'Azemar P, et al. Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. Thromb Haemost. 1996;75:233-8.
473. Agnelli G, Piovella F, Buoncristiani P, Severi P, Pini M, D'Angelo A, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. N Engl J Med. 1998;339:80-5.
474. Iorio A, Agnelli G. Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery: a meta-analysis. Arch Intern Med. 2000;160:2327-32.
475. Goldhaber SZ, Turpie AG. Prevention of venous thromboembolism among hospitalized medical patients. Circulation. 2005;111:e1-3.
476. Alikhan R, Cohen AT, Combe S, Samama MM, Desjardins L, Eldor A, et al. Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. Arch Intern Med. 2004;164:963-8.
477. Monreal M, Alastrue A, Rull M, Mira X, Muxart J, Rosell R, et al. Upper extremity deep venous thrombosis in cancer patients with venous access devices—prophylaxis with a low molecular weight heparin (Fragmin). Thromb Haemost. 1996;75:251-3.
478. Levine MN, Gent M, Hirsh J, Arnold A, Goodyear MD, Hryniuk W, et al. The thrombogenic effect of anticancer drug therapy in women with stage II breast cancer. N Engl J Med. 1988;318:404-7.
479. Goldhaber SZ, Tapson VF. A prospective registry of 5,451 patients with ultrasound-

confirmed deep vein thrombosis. Am J Cardiol. 2004;93:259-62.
480. Goodnough LT, Saito H, Manni A, Jones PK, Pearson OH. Increased incidence of thromboembolism in stage IV breast cancer patients treated with a five-drug chemotherapy regimen. A study of 159 patients. Cancer. 1984;54:1264-8.
481. Spyropoulos AC. Emerging strategies in the prevention of venous thromboembolism in hospitalized medical patients. Chest. 2005;128:958-69.
482. Zakai NA, Wright J, Cushman M. Risk factors for venous thrombosis in medical inpatients: validation of a thrombosis risk score. J Thromb Haemost. 2004;2:2156-61.
483. Hirsch DR, Ingenito EP, Goldhaber SZ. Prevalence of deep venous thrombosis among patients in medical intensive care. JAMA. 1995;274:335-7.
484. Geerts W, Selby R. Prevention of venous thromboembolism in the ICU. Chest. 2003;124:357S-63S.
485. Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. Circulation. 2004;110:874-9.
486. Cohen AT. Venous thromboembolic disease management of the nonsurgical moderate- and high-risk patient. Semin Hematol. 2000;37:19-22.
487. Halkin H, Goldberg J, Modan M, Modan B. Reduction of mortality in general medical in-patients by low-dose heparin prophylaxis. Ann Intern Med. 1982;96:561-5.
488. Gardlund B. Randomised, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases. The Heparin Prophylaxis Study Group. Lancet. 1996;347:1357-61.
489. Leizorovicz A, Kassai B, Becker F, Cucherat M. The assessment of deep vein thromboses for therapeutic trials. Angiology. 2003;54:19-24.
490. Bergmann JF, Neuhart E. A multicenter randomized double-blind study of enoxaparin compared with unfractionated heparin in the prevention of venous thromboembolic disease in elderly in-patients bedridden for an acute medical illness. The Enoxaparin in Medicine Study Group. Thromb Haemost. 1996;76:529-34.
491. Harenberg J, Roebruck P, Heene DL. Subcutaneous low-molecular-weight heparin versus standard heparin and the prevention of thromboembolism in medical inpatients. The Heparin Study in Internal Medicine Group. Haemostasis. 1996;26:127-39.
492. Lechler E, Schramm W, Flosbach CW. The venous thrombotic risk in non-surgical patients: epidemiological data and efficacy/safety profile of a low-molecular-weight heparin (enoxaparin). The Prime Study Group. Haemostasis. 1996;26 Suppl 2:49-56.
493. Kleber FX, Witt C, Vogel G, Koppenhagen K, Schomaker U, Flosbach CW. Randomized comparison of enoxaparin with unfractionated heparin for the prevention of venous thromboembolism in medical patients with heart failure or severe respiratory disease. Am Heart J. 2003;145:614-21.
494. Mismetti P, Laporte-Simitsidis S, Tardy B, Cucherat M, Buchmuller A, Juillard-Delsart D, et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. Thromb Haemost. 2000;83:14-9.
495. Cohen AT, Davidson BL, Gallus AS, Lassen MR, Prins MH, Tomkowski W, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. Br Med J. 2006;332:325-9.
496. Goldhaber SZ, Dunn K, MacDougall RC. New onset of venous thromboembolism among

hospitalized patients at Brigham and Women's Hospital is caused more often by prophylaxis failure than by withholding treatment. Chest. 2000;118:1680-4.
497. Eikelboom JW, Mazzarol A, Quinlan DJ, Beaver R, Williamson J, Yi Q, et al. Thromboprophylaxis practice patterns in two Western Australian teaching hospitals. Haematologica. 2004;89:586-93.
498. Bath PM, Iddenden R, Bath FJ. Low-molecular-weight heparins and heparinoids in acute ischemic stroke : a meta-analysis of randomized controlled trials. Stroke. 2000;31:1770-8.
499. Dumas R, Woitinas F, Kutnowski M, Nikolic I, Berberich R, Abedinpour F, et al. A multicentre, double-blind, randomized study to compare the safety and efficacy of once-daily ORG 10172 and twice-daily low-dose heparin in preventing deep-vein thrombosis in patients with acute ischaemic stroke. Age Ageing. 1994;23:512-6.
500. Turpie AG, Gent M, Cote R, Levine MN, Ginsberg JS, Powers PJ, et al. A low-molecular-weight heparinoid compared with unfractionated heparin in the prevention of deep vein thrombosis in patients with acute ischemic stroke. A randomized, double-blind study. Ann Intern Med. 1992;117:353-7.
501. Hillbom M, Erila T, Sotaniemi K, Tatlisumak T, Sarna S, Kaste M. Enoxaparin vs heparin for prevention of deep-vein thrombosis in acute ischaemic stroke: a randomized, double-blind study. Acta Neurol Scand. 2002;106:84-92.
502. Counsell C, Sandercock P. Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischemic stroke (Cochrane review). Stroke. 2002;33:1925-6.
503. Geerts W, Cook D, Selby R, Etchells E. Venous thromboembolism and its prevention in critical care. J Crit Care. 2002;17:95-104.
504. Cook D, Attia J, Weaver B, McDonald E, Meade M, Crowther M. Venous thromboembolic disease: an observational study in medical-surgical intensive care unit patients. J Crit Care. 2000;15:127-32.
505. Harris LM, Curl GR, Booth FV, Hassett JM, Jr., Leney G, Ricotta JJ. Screening for asymptomatic deep vein thrombosis in surgical intensive care patients. J Vasc Surg. 1997;26:764-9.
506. Cook D, McMullin J, Hodder R, Heule M, Pinilla J, Dodek P, et al. Prevention and diagnosis of venous thromboembolism in critically ill patients: a Canadian survey. Crit Care. 2001;5:336-42.
507. Ibrahim EH, Iregui M, Prentice D, Sherman G, Kollef MH, Shannon W. Deep vein thrombosis during prolonged mechanical ventilation despite prophylaxis. Crit Care Med. 2002;30:771-4.
508. Marik PE, Andrews L, Maini B. The incidence of deep venous thrombosis in ICU patients. Chest. 1997;111:661-4.
509. Kapoor M, Kupfer YY, Tessler S. Subcutaneous heparin prophylaxis significantly reduces the incidence of venous thromboembolic evnts in the critically ill (abstr). Crit Care Med. 1999;27(suppl):A69.
510. Goldhaber SZ, Kett DH, Cusumano CJ. Low molecural weight heparin versus minidose unfractionated heparin for prophylaxis against venous thromboembolism in medical intensive care unit patients: a randomized controlled trial. J Am Coll Cardiol. 2000;35(suppl):325A.
511. Levitan N, Dowlati A, Remick SC, Tahsildar HI, Sivinski LD, Beyth R, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus

those without malignancy. Risk analysis using Medicare claims data. Medicine (Baltimore). 1999;78:285-91.
512. Koopman MM, Prandoni P, Piovella F, Ockelford PA, Brandjes DP, van der Meer J, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. N Engl J Med. 1996;334:682-7.
513. Sifontes MT, Nuss R, Hunger SP, Wilimas J, Jacobson LJ, Manco-Johnson MJ. The factor V Leiden mutation in children with cancer and thrombosis. Br J Haematol. 1997;96:484-9.
514. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. The Columbus Investigators. N Engl J Med. 1997;337:657-62.
515. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90:1371-88.
516. Fisher B, Redmond C, Legault-Poisson S, Dimitrov NV, Brown AM, Wickerham DL, et al. Postoperative chemotherapy and tamoxifen compared with tamoxifen alone in the treatment of positive-node breast cancer patients aged 50 years and older with tumors responsive to tamoxifen: results from the National Surgical Adjuvant Breast and Bowel Project B-16. J Clin Oncol. 1990;8:1005-18.
517. Pritchard KI, Paterson AH, Paul NA, Zee B, Fine S, Pater J. Increased thromboembolic complications with concurrent tamoxifen and chemotherapy in a randomized trial of adjuvant therapy for women with breast cancer. National Cancer Institute of Canada Clinical Trials Group Breast Cancer Site Group. J Clin Oncol. 1996;14:2731-7.
518. Weiss RB, Tormey DC, Holland JF, Weinberg VE. Venous thrombosis during multimodal treatment of primary breast carcinoma. Cancer Treat Rep. 1981;65:677-9.
519. Clahsen PC, van de Velde CJ, Julien JP, Floiras JL, Mignolet FY. Thromboembolic complications after perioperative chemotherapy in women with early breast cancer: a European Organization for Research and Treatment of Cancer Breast Cancer Cooperative Group study. J Clin Oncol. 1994;12:1266-71.
520. Saphner T, Tormey DC, Gray R. Venous and arterial thrombosis in patients who received adjuvant therapy for breast cancer. J Clin Oncol. 1991;9:286-94.
521. Rivkin SE, Green S, Metch B, Cruz AB, Abeloff MD, Jewell WR, et al. Adjuvant CMFVP versus tamoxifen versus concurrent CMFVP and tamoxifen for postmenopausal, node-positive, and estrogen receptor-positive breast cancer patients: a Southwest Oncology Group study. J Clin Oncol. 1994;12:2078-85.
522. Weijl NI, Rutten MF, Zwinderman AH, Keizer HJ, Nooy MA, Rosendaal FR, et al. Thromboembolic events during chemotherapy for germ cell cancer: a cohort study and review of the literature. J Clin Oncol. 2000;18:2169-78.
523. Ottinger H, Belka C, Kozole G, Engelhard M, Meusers P, Paar D, et al. Deep venous thrombosis and pulmonary artery embolism in high-grade non Hodgkin's lymphoma: incidence, causes and prognostic relevance. Eur J Haematol. 1995;54:186-94.
524. Clarke CS, Otridge BW, Carney DN. Thromboembolism. A complication of weekly chemotherapy in the treatment of non-Hodgkin's lymphoma. Cancer. 1990;66:2027-30.
525. von Tempelhoff GF, Harenberg J, Niemann F, Hommel G, Kirkpatrick CJ, Heilmann L. Effect of low molecular weight heparin (Certoparin) versus unfractionated heparin on cancer survival following breast and pelvic cancer surgery: A prospective randomized double-blind trial. Int J Oncol. 2000;16:815-24.

526. Thodiyil PA, Walsh DC, Kakkar AK. Thromboprophylaxis in the cancer patient. Acta Haematol. 2001;106:73-80.
527. Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med. 2002;346:975-80.
528. Levine M, Hirsh J, Gent M, Arnold A, Warr D, Falanga A, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. Lancet. 1994;343:886-9.
529. Bern MM, Lokich JJ, Wallach SR, Bothe A, Jr., Benotti PN, Arkin CF, et al. Very low doses of warfarin can prevent thrombosis in central venous catheters. A randomized prospective trial. Ann Intern Med. 1990;112:423-8.
530. Heaton DC, Han DY, Inder A. Minidose (1 mg) warfarin as prophylaxis for central vein catheter thrombosis. Intern Med J. 2002;32:84-8.
531. Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. J Clin Oncol. 2003;21:3665-75.
532. Walshe LJ, Malak SF, Eagan J, Sepkowitz KA. Complication rates among cancer patients with peripherally inserted central catheters. J Clin Oncol. 2002;20:3276-81.
533. Couban S, Goodyear M, Burnell M, Dolan S, Wasi P, Barnes D, et al. Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. J Clin Oncol. 2005;23:4063-9.
534. Samama MM, Conard J, Horellou MH, Toulemonde F. Coangulation abnormalities predisposing to the development of deep vein thrombosis. In: Comerota AJ, Bergqvist D, Nicolaides AN, Scurr JH, eds. Prevention of venous thromboembolism. London: Med-Orion; 1994:43-56.
535. Egeberg O. Inherited Antithrombin Deficiency Causing Thrombophilia. Thromb Diath Haemorrh. 1965;13:516-30.
536. Engesser L, Broekmans AW, Briet E, Brommer EJ, Bertina RM. Hereditary protein S deficiency: clinical manifestations. Ann Intern Med. 1987;106:677-82.
537. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994;369:64-7.
538. Dahlback B, Carlsson M, Svensson PJ. Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: prediction of a cofactor to activated protein C. Proc Natl Acad Sci U S A. 1993;90:1004-8.
539. Svensson PJ, Dahlback B. Resistance to activated protein C as a basis for venous thrombosis. N Engl J Med. 1994;330:517-22.
540. Trossaert M, Conard J, Horellou MH, Samaha M, Elalamy I, Samama MM. Resistance to activated protein C in venous thromboembolic complications. Incidence and clinical manifestations. Presse Med. 1995;24:209-12.
541. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood. 1996;88:3698-703.
542. Grandone E, Margaglione M, Colaizzo D, D'Andrea G, Cappucci G, Brancaccio V, et al. Genetic susceptibility to pregnancy-related venous thromboembolism: roles of factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T

mutations. Am J Obstet Gynecol. 1998;179:1324-8.
543. De Stefano V, Rossi E, Paciaroni K, Leone G. Screening for inherited thrombophilia: indications and therapeutic implications. Haematologica. 2002;87:1095-108.
544. Bertina RM, van der Linden IK, Engesser L, Muller HP, Brommer EJ. Hereditary heparin cofactor II deficiency and the risk of development of thrombosis. Thromb Haemost. 1987;57:196-200.
545. van der Meer FJ, Koster T, Vandenbroucke JP, Briet E, Rosendaal FR. The Leiden Thrombophilia Study (LETS). Thromb Haemost. 1997;78:631-5.
546. Broekmans AW, Conard J, van Weyenberg RG, Horellou MH, Kluft C, Bertina RM. Treatment of hereditary protein C deficiency with stanozolol. Thromb Haemost. 1987;57:20-4.
547. Eichinger S, Schonauer V, Weltermann A, Minar E, Bialonczyk C, Hirschl M, et al. Thrombin-activatable fibrinolysis inhibitor and the risk for recurrent venous thromboembolism. Blood. 2004;103:3773-6.
548. Kostka H, Kuhlisch E, Schellong S, Siegert G. Polymorphisms in the TAFI gene and the risk of venous thrombosis. Clin Lab. 2003;49:645-7.
549. Lisman T, de Groot PG, Meijers JC, Rosendaal FR. Reduced plasma fibrinolytic potential is a risk factor for venous thrombosis. Blood. 2005;105:1102-5.
550. Kyrle PA, Minar E, Hirschl M, Bialonczyk C, Stain M, Schneider B, et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. N Engl J Med. 2000;343:457-62.
551. Tripodi A. Levels of coagulation factors and venous thromboembolism. Haematologica. 2003;88:705-11.
552. Koster T, Blann AD, Briet E, Vandenbroucke JP, Rosendaal FR. Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis. Lancet. 1995;345:152-5.
553. Meijers JC, Tekelenburg WL, Bouma BN, Bertina RM, Rosendaal FR. High levels of coagulation factor XI as a risk factor for venous thrombosis. N Engl J Med. 2000;342:696-701.
554. Kamphuisen PW, Eikenboom JC, Rosendaal FR, Koster T, Blann AD, Vos HL, et al. High factor VIII antigen levels increase the risk of venous thrombosis but are not associated with polymorphisms in the von Willebrand factor and factor VIII gene. Br J Haematol. 2001;115:156-8.
555. Weltermann A, Eichinger S, Bialonczyk C, Minar E, Hirschl M, Quehenberger P, et al. The risk of recurrent venous thromboembolism among patients with high factor IX levels. J Thromb Haemost. 2003;1:28-32.
556. Vossen CY, Conard J, Fontcuberta J, Makris M, Van Der Meer FJ, Pabinger I, et al. Familial thrombophilia and lifetime risk of venous thrombosis. J Thromb Haemost. 2004;2:1526-32.
557. Makris M, Leach M, Beauchamp NJ, Daly ME, Cooper PC, Hampton KK, et al. Genetic analysis, phenotypic diagnosis, and risk of venous thrombosis in families with inherited deficiencies of protein S. Blood. 2000;95:1935-41.
558. Samama MM, Dahl OE, Quinlan DJ, Mismetti P, Rosencher N. Quantification of risk factors for venous thromboembolism: a preliminary study for the development of a risk assessment tool. Haematologica. 2003;88:1410-21.
559. Wahl DG, Guillemin F, de Maistre E, Perret C, Lecompte T, Thibaut G. Risk for venous

thrombosis related to antiphospholipid antibodies in systemic lupus erythematosus—a meta-analysis. Lupus. 1997;6:467-73.
560. Wahl DG, De Maistre E, Guillemin F, Regnault V, Perret-Guillaume C, Lecompte T. Antibodies against phospholipids and beta 2-glycoprotein I increase the risk of recurrent venous thromboembolism in patients without systemic lupus erythematosus. QJM. 1998;91:125-30.
561. Wahl DG, Guillemin F, de Maistre E, Perret-Guillaume C, Lecompte T, Thibaut G. Meta-analysis of the risk of venous thrombosis in individuals with antiphospholipid antibodies without underlying autoimmune disease or previous thrombosis. Lupus. 1998;7:15-22.
562. Galli M, Luciani D, Bertolini G, Barbui T. Anti-beta 2-glycoprotein I, antiprothrombin antibodies, and the risk of thrombosis in the antiphospholipid syndrome. Blood. 2003;102:2717-23.
563. de Groot PG, Lutters B, Derksen RH, Lisman T, Meijers JC, Rosendaal FR. Lupus anticoagulants and the risk of a first episode of deep venous thrombosis. J Thromb Haemost. 2005;3:1993-7.
564. Wehmeier A, Sudhoff T, Meierkord F. Relation of platelet abnormalities to thrombosis and hemorrhage in chronic myeloproliferative disorders. Semin Thromb Hemost. 1997;23:391-402.
565. Toh CH. Characterization of thrombin activatable fibrinolysis inhibitor in normal and acquired haemostatic dysfunction. Blood Coagul Fibrinolysis. 2003;14 Suppl 1:S69-71.
566. Kraaijenhagen RA, in't Anker PS, Koopman MM, Reitsma PH, Prins MH, van den Ende A, et al. High plasma concentration of factor VIIIc is a major risk factor for venous thromboembolism. Thromb Haemost. 2000;83:5-9.
567. Legnani C, Cini M, Cosmi B, Poggi M, Boggian O, Palareti G. Risk of deep vein thrombosis: interaction between oral contraceptives and high factor VIII levels. Haematologica. 2004;89:1347-51.
568. van den Belt AG, Hutten BA, Prins MH, Bossuy PM. Duration of oral anticoagulant treatment in patients with venous thromboembolism and a deficiency of antithrombin, protein C or protein S—a decision analysis. Thromb Haemost. 2000;84:758-63.
569. Palareti G, Legnani C, Cosmi B, Valdre L, Lunghi B, Bernardi F, et al. Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation. 2003;108:313-8.
570. Palareti G, Legnani C, Cosmi B, Guazzaloca G, Pancani C, Coccheri S. Risk of venous thromboembolism recurrence: high negative predictive value of D-dimer performed after oral anticoagulation is stopped. Thromb Haemost. 2002;87:7-12.
571. Prandoni P, Lensing AW, Prins MH, Bernardi E, Marchiori A, Bagatella P, et al. Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. Ann Intern Med. 2002;137:955-60.
572. Lechner K, Korninger C, Kyrle P, Geissler K, Niessner H, Pabinger I, et al. Oral anticoagulant therapy—renaissance of an old therapy?. Wien Klin Wochenschr. 1987;99:203-10.
573. Triplett DA. Antiphospholipid antibodies, lupus anticoagulants and thromboembolic disease. Haematologica. 1995;80:122-6.
574. Ginsburg KS, Liang MH, Newcomer L, Goldhaber SZ, Schur PH, Hennekens CH, et al. Anticardiolipin antibodies and the risk for ischemic stroke and venous thrombosis. Ann

Intern Med. 1992;117:997-1002.
575. Schulman S, Granqvist S, Holmstrom M, Carlsson A, Lindmarker P, Nicol P, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. N Engl J Med. 1997;336:393-8.
576. Lindahl TL, Lundahl TH, Nilsson L, Andersson CA. APC-resistance is a risk factor for postoperative thromboembolism in elective replacement of the hip or knee—a prospective study. Thromb Haemost. 1999;81:18-21.
577. Ryan DH, Crowther MA, Ginsberg JS, Francis CW. Relation of factor V Leiden genotype to risk for acute deep venous thrombosis after joint replacement surgery. Ann Intern Med. 1998;128:270-6.
578. Wahlander K, Larson G, Lindahl TL, Andersson C, Frison L, Gustafsson D, et al. Factor V Leiden (G1691A) and prothrombin gene G20210A mutations as potential risk factors for venous thromboembolism after total hip or total knee replacement surgery. Thromb Haemost. 2002;87:580-5.
579. Vossen CY, Walker ID, Svensson P, Souto JC, Scharrer I, Preston FE, et al. Recurrence rate after a first venous thrombosis in patients with familial thrombophilia. Arterioscler Thromb Vasc Biol. 2005;25:1992-7.
580. Salzman EW, Davies GC. Prophylaxis of venous thromboembolism: analysis of cost effectiveness. Ann Surg. 1980;191:207-18.
581. Oster G, Tuden RL, Colditz GA. Prevention of venous thromboembolism after general surgery. Cost-effectiveness analysis of alternative approaches to prophylaxis. Am J Med. 1987;82:889-99.
582. Oster G, Tuden RL, Colditz GA. A cost-effectiveness analysis of prophylaxis against deep-vein thrombosis in major orthopedic surgery. JAMA. 1987;257:203-8.
583. Bergqvist D, Jendteg S, Lindgren B, Matzsch T, Persson U. The economics of general thromboembolic prophylaxis. World J Surg. 1988;12:349-55.
584. Bergqvist D, Matzsch T, Jendteg S, Lindgren B, Persson U. The cost-effectiveness of prevention of post-operative thromboembolism. Acta Chir Scand Suppl. 1990;556:36-41.
585. Hull RD, Hirsh J, Sackett DL, Stoddart GL. Cost-effectiveness of primary and secondary prevention of fatal pulmonary embolism in high-risk surgical patients. Can Med Assoc J. 1982;127:990-5.
586. Gould MK, Dembitzer AD, Sanders GD, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis. Ann Intern Med. 1999;130:789-99.
587. Maxwell GL, Myers ER, Clarke-Pearson DL. Cost-effectiveness of deep venous thrombosis prophylaxis in gynecologic oncology surgery. Obstet Gynecol. 2000;95:206-14.
588. Dainty L, Maxwell GL, Clarke-Pearson DL, Myers ER. Cost-effectiveness of combination thromboembolism prophylaxis in gynecologic oncology surgery. Gynecol Oncol. 2004;93:366-73.
589. Hull RD, Raskob GE, Rosenbloom D, Pineo GF, Lerner RG, Gafni A, et al. Treatment of proximal vein thrombosis with subcutaneous low-molecular-weight heparin vs intravenous heparin. An economic perspective. Arch Intern Med. 1997;157:289-94.
590. Amorosi SL, Tsilimingras K, Thompson D, Fanikos J, Weinstein MC, Goldhaber SZ. Cost analysis of “bridging therapy” with low-molecular-weight heparin versus unfractionated heparin during temporary interruption of chronic anticoagulation. Am J Cardiol.

2004;93:509-11.
591. Spyropoulos AC, Frost FJ, Hurley JS, Roberts M. Costs and clinical outcomes associated with low-molecular-weight heparin vs unfractionated heparin for perioperative bridging in patients receiving long-term oral anticoagulant therapy. Chest. 2004;125:1642-50.
592. McGarry LJ, Thompson D, Weinstein MC, Goldhaber SZ. Cost effectiveness of thromboprophylaxis with a low-molecular-weight heparin versus unfractionated heparin in acutely ill medical inpatients. Am J Manag Care. 2004;10:632-42.
593. Zierler BK. Ultrasonography and diagnosis of venous thromboembolism. Circulation. 2004;109:I9-14.
594. Wells PS, Anderson DR, Rodger M, Stiell I, Dreyer JF, Barnes D, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med. 2001;135:98-107.
595. Wells PS, Anderson DR, Rodger M, Forgie M, Kearon C, Dreyer J, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003;349:1227-35.
596. Schoepf UJ, Kucher N, Kipfmueller F, Quiroz R, Costello P, Goldhaber SZ. Right ventricular enlargement on chest computed tomography: a predictor of early death in acute pulmonary embolism. Circulation. 2004;110:3276-80.
597. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:401S-28S.
598. Brandjes DP, Heijboer H, Buller HR, de Rijk M, Jagt H, ten Cate JW. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. N Engl J Med. 1992;327:1485-9.
599. Hull RD, Raskob GE, Rosenbloom D, Lemaire J, Pineo GF, Baylis B, et al. Optimal therapeutic level of heparin therapy in patients with venous thrombosis. Arch Intern Med. 1992;152:1589-95.
600. Brill-Edwards P, Ginsberg JS, Johnston M, Hirsh J. Establishing a therapeutic range for heparin therapy. Ann Intern Med. 1993;119:104-9.
601. Burotto M, Gabrielli L, Crossley N. [Critical appraisal: Subcutaneous adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism. Prandoni P, Carnovali M, Marchiori A, Galilei investigators. Arch Intern Med 2004; 164: 1077-83]. Rev Med Chil. 2004;132:1140-3.
602. Albada J, Nieuwenhuis HK, Sixma JJ. Treatment of acute venous thromboembolism with low molecular weight heparin (Fragmin). Results of a double-blind randomized study. Circulation. 1989;80:935-40.
603. Bratt G, Aberg W, Johansson M, Tornebohm E, Granqvist S, Lockner D. Two daily subcutaneous injections of fragmin as compared with intravenous standard heparin in the treatment of deep venous thrombosis (DVT). Thromb Haemost. 1990;64:506-10.
604. A randomised trial of subcutaneous low molecular weight heparin (CY 216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. A collaborative European multicentre study. Thromb Haemost. 1991;65:251-6.
605. Breddin HK, Hach-Wunderle V, Nakov R, Kakkar VV. Effects of a low-molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. N Engl J Med. 2001;344:626-31.

606. Hull RD, Raskob GE, Pineo GF, Green D, Trowbridge AA, Elliott CG, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med. 1992;326:975-82.
607. Prandoni P, Lensing AW, Buller HR, Carta M, Cogo A, Vigo M, et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. Lancet. 1992;339:441-5.
608. Lopaciuk S, Meissner AJ, Filipecki S, Zawilska K, Sowier J, Ciesielski L, et al. Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: a Polish multicenter trial. Thromb Haemost. 1992;68:14-8.
609. Simonneau G, Charbonnier B, Decousus H, Planchon B, Ninet J, Sie P, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. Arch Intern Med. 1993;153:1541-6.
610. Lindmarker P, Holmstrom M, Granqvist S, Johnsson H, Lockner D. Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. Thromb Haemost. 1994;72:186-90.
611. Monreal M, Lafoz E, Olive A, del Rio L, Vedia C. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. Thromb Haemost. 1994;71:7-11.
612. Alhenc-Gelas M, Jestin-Le Guernic C, Vitoux JF, Kher A, Aiach M, Fiessinger JN. Adjusted versus fixed doses of the low-molecular-weight heparin fragmin in the treatment of deep vein thrombosis. Fragmin-Study Group. Thromb Haemost. 1994;71:698-702.
613. Simonneau G, Sors H, Charbonnier B, Page Y, Laaban JP, Azarian R, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire. N Engl J Med. 1997;337:663-9.
614. Findik S, Erkan ML, Selcuk MB, Albayrak S, Atici AG, Doru F. Low-molecular-weight heparin versus unfractionated heparin in the treatment of patients with acute pulmonary thromboembolism. Respiration. 2002;69:440-4.
615. Charbonnier BA, Fiessinger JN, Banga JD, Wenzel E, d'Azemar P, Sagnard L. Comparison of a once daily with a twice daily subcutaneous low molecular weight heparin regimen in the treatment of deep vein thrombosis. FRAXODI group. Thromb Haemost. 1998;79:897-901.
616. Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. Ann Intern Med. 2001;134:191-202.
617. Couturaud F, Julian JA, Kearon C. Low molecular weight heparin administered once versus twice daily in patients with venous thromboembolism: a meta-analysis. Thromb Haemost. 2001;86:980-4.
618. Harenberg J, Riess H, Buller HR, Brom J, Weidinger G, Huisman MV. Comparison of six-month outcome of patients initially treated for acute deep vein thrombosis with a low molecular weight heparin Certoparin at a fixed, body-weight-independent dosage or unfractionated heparin. Haematologica. 2003;88:1157-62.
619. Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, et al. A comparison of low-

molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med. 1996;334:677-81.
620. Lapidus L, Borretzen J, Fahlen M, Thomsen HG, Hasselblom S, Larson L, et al. Home treatment of deep vein thrombosis. An out-patient treatment model with once-daily injection of low-molecular-weight heparin (tinzaparin) in 555 patients. Pathophysiol Haemost Thromb. 2002;32:59-66.
621. Rodger MA, Gagne-Rodger C, Howley HE, Carrier M, Coyle D, Wells PS. The outpatient treatment of deep vein thrombosis delivers cost savings to patients and their families, compared to inpatient therapy. Thromb Res. 2003;112:13-8.
622. Segal JB, Bolger DT, Jenckes MW, Krishnan JA, Streiff MB, Eng J, et al. Outpatient therapy with low molecular weight heparin for the treatment of venous thromboembolism: a review of efficacy, safety, and costs. Am J Med. 2003;115:298-308.
623. Spyropoulos AC, Hurley JS, Ciesla GN, de Lissovoy G. Management of acute proximal deep vein thrombosis: pharmacoeconomic evaluation of outpatient treatment with enoxaparin vs inpatient treatment with unfractionated heparin. Chest. 2002;122:108-14.
624. Boccalon H, Elias A, Chale JJ, Cadene A, Gabriel S. Clinical outcome and cost of hospital vs home treatment of proximal deep vein thrombosis with a low-molecular-weight heparin: the Vascular Midi-Pyrenees study. Arch Intern Med. 2000;160:1769-73.
625. Dunn AS, Schechter C, Gotlin A, Vomvolakis D, Jacobs E, Sacks HS, et al. Outpatient treatment of deep venous thrombosis in diverse inner-city patients. Am J Med. 2001;110:458-62.
626. Schwarz T, Schmidt B, Hohlein U, Beyer J, Schroder HE, Schellong SM. Eligibility for home treatment of deep vein thrombosis: prospective study. Br Med J. 2001;322:1212-3.
627. Buller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. Ann Intern Med. 2004;140:867-73.
628. Buller HR, Davidson BL, Decousus H, Gallus A, Gent M, Piovella F, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med. 2003;349:1695-702.
629. Schulman S, Lundstrom T, Walander K, Billing Clason S, Eriksson H. Ximelagatran for the secondary prevention of venous thromboembolism: a complementary follow-up analysis of the THRIVE III study. Thromb Haemost. 2005;94:820-4.
630. Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med. 1999;340:901-7.
631. Kearon C, Ginsberg JS, Kovacs MJ, Anderson DR, Wells P, Julian JA, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med. 2003;349:631-9.
632. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med. 2003;348:1425-34.
633. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. Ann Intern Med. 1994;120:897-902.
634. Hull R, Hirsh J, Jay R, Carter C, England C, Gent M, et al. Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. N Engl J Med.

1982;307:1676-81.
635. Koo S, Kucher N, Nguyen PL, Fanikos J, Marks PW, Goldhaber SZ. The effect of excessive anticoagulation on mortality and morbidity in hospitalized patients with anticoagulant-related major hemorrhage. Arch Intern Med. 2004;164:1557-60.
636. Hull RD, Raskob GE, Rosenbloom D, Panju AA, Brill-Edwards P, Ginsberg JS, et al. Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. N Engl J Med. 1990;322:1260-4.
637. Gallus A, Jackaman J, Tillett J, Mills W, Wycherley A. Safety and efficacy of warfarin started early after submassive venous thrombosis or pulmonary embolism. Lancet. 1986;2:1293-6.
638. Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Larfars G, Nicol P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group. N Engl J Med. 1995;332:1661-5.
639. Kearon C, Ginsberg JS, Anderson DR, Kovacs MJ, Wells P, Julian JA, et al. Comparison of 1 month with 3 months of anticoagulation for a first episode of venous thromboembolism associated with a transient risk factor. J Thromb Haemost. 2004;2:743-9.
640. Levine MN, Hirsh J, Gent M, Turpie AG, Weitz J, Ginsberg J, et al. Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. Thromb Haemost. 1995;74:606-11.
641. Hyers TM, Agnelli G, Hull RD, Weg JG, Morris TA, Samama M, et al. Antithrombotic therapy for venous thromboembolic disease. Chest. 1998;114:561S-78S.
642. Seshadri N, Goldhaber SZ, Elkayam U, Grimm RA, Groce JB, 3rd, Heit JA, et al. The clinical challenge of bridging anticoagulation with low-molecular-weight heparin in patients with mechanical prosthetic heart valves: an evidence-based comparative review focusing on anticoagulation options in pregnant and nonpregnant patients. Am Heart J. 2005;150:27-34.
643. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349:146-53.
644. Pinede L, Ninet J, Duhaut P, Chabaud S, Demolombe-Rague S, Durieu I, et al. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. Circulation. 2001;103:2453-60.
645. Lagerstedt CI, Olsson CG, Fagher BO, Oqvist BW, Albrechtsson U. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. Lancet. 1985;2:515-8.
646. Brandjes DP, Buller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet. 1997;349:759-62.
647. Prandoni P, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. Ann Intern Med. 2004;141:249-56.
648. Partsch H, Kaulich M, Mayer W. Immediate mobilisation in acute vein thrombosis reduces post-thrombotic syndrome. Int Angiol. 2004;23:206-12.

649. Partsch H, Blattler W. Compression and walking versus bed rest in the treatment of proximal deep venous thrombosis with low molecular weight heparin. J Vasc Surg. 2000;32:861-9.
650. Blattler W, Partsch H. Leg compression and ambulation is better than bed rest for the treatment of acute deep venous thrombosis. Int Angiol. 2003;22:393-400.
651. Gerlach AT, Pickworth KK, Seth SK, Tanna SB, Barnes JF. Enoxaparin and bleeding complications: a review in patients with and without renal insufficiency. Pharmacotherapy. 2000;20:771-5.
652. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:188S-203S.
653. Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes Garcia M, Arriaga-Nava R, Valencia S, Rosado-Buzzo A, et al. Streptokinase and Heparin versus Heparin Alone in Massive Pulmonary Embolism: A Randomized Controlled Trial. J Thromb Thrombolysis. 1995;2:227-29.
654. Goldhaber SZ. A contemporary approach to thrombolytic therapy for pulmonary embolism. Vasc Med. 2000;5:115-23.
655. Sharma GV, Folland ED, McIntyre KM, Sasahara AA. Long-term benefit of thrombolytic therapy in patients with pulmonary embolism. Vasc Med. 2000;5:91-5.
656. Kanter DS, Mikkola KM, Patel SR, Parker JA, Goldhaber SZ. Thrombolytic therapy for pulmonary embolism. Frequency of intracranial hemorrhage and associated risk factors. Chest. 1997;111:1241-5.
657. Goldhaber SZ. Pulmonary Embolism Thrombolysis Improves Survival in Massive Pulmonary Embolism. J Thromb Thrombolysis. 1995;2:219-20.
658. Kucher N, Wallmann D, Carone A, Windecker S, Meier B, Hess OM. Incremental prognostic value of troponin I and echocardiography in patients with acute pulmonary embolism. Eur Heart J. 2003;24:1651-6.
659. Grifoni S, Olivotto I, Cecchini P, Pieralli F, Camaiti A, Santoro G, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation. 2000;101:2817-22.
660. Ribeiro A, Lindmarker P, Juhlin-Dannfelt A, Johnsson H, Jorfeldt L. Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. Am Heart J. 1997;134:479-87.
661. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet. 1999;353:1386-9.
662. Goldhaber SZ, Haire WD, Feldstein ML, Miller M, Toltzis R, Smith JL, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet. 1993;341:507-11.
663. S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med. 2002;347:1143-50.
664. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Prognostic role of echocardiography among patients with acute pulmonary embolism and a systolic arterial pressure of 90 mm Hg or higher. Arch Intern Med. 2005;165:1777-81.
665. Kucher N, Windecker S, Banz Y, Schmitz-Rode T, Mettler D, Meier B, et al. Percutaneous catheter thrombectomy device for acute pulmonary embolism: in vitro and in vivo testing.

Radiology. 2005;236:852-8.
666. Aklog L, Williams CS, Byrne JG, Goldhaber SZ. Acute pulmonary embolectomy: a contemporary approach. Circulation. 2002;105:1416-9.
667. Leacche M, Unic D, Goldhaber SZ, Rawn JD, Aranki SF, Couper GS, et al. Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. J Thorac Cardiovasc Surg. 2005;129:1018-23.
668. Arnesen H, Heilo A, Jakobsen E, Ly B, Skaga E. A prospective study of streptokinase and heparin in the treatment of deep vein thrombosis. Acta Med Scand. 1978;203:457-63.
669. Jeffery P, Immelman E, Amoore J. Treatment of deep vein thrombosis with heparin or streptokinase: Long term venous function assessment. (abstr). In: Proceedings of the 2nd International vascular Symposium. London; 1986:S20.3.
670. Goldhaber SZ, Buring JE, Lipnick RJ, Hennekens CH. Pooled analyses of randomized trials of streptokinase and heparin in phlebographically documented acute deep venous thrombosis. Am J Med. 1984;76:393-7.
671. Comerota AJ, Aldridge SC. Thrombolytic therapy for deep venous thrombosis: a clinical review. Can J Surg. 1993;36:359-64.
672. Semba CP, Dake MD. Iliofemoral deep venous thrombosis: aggressive therapy with catheter-directed thrombolysis. Radiology. 1994;191:487-94.
673. Marache P, Asseman P, Jabinet JL, Prat A, Bauchart JJ, Aisenfarb JC, et al. Percutaneous transluminal venous angioplasty in occlusive iliac vein thrombosis resistant to thrombolysis. Am Heart J. 1993;125:362-6.
674. Comerota AJ, Throm RC, Mathias SD, Haughton S, Mewissen M. Catheter-directed thrombolysis for iliofemoral deep venous thrombosis improves health-related quality of life. J Vasc Surg. 2000;32:130-7.
675. Elsharawy M, Elzayat E. Early results of thrombolysis vs anticoagulation in iliofemoral venous thrombosis. A randomised clinical trial. Eur J Vasc Endovasc Surg. 2002;24:209-14.
676. Kucher N, Goldhaber SZ. Management of massive pulmonary embolism. Circulation. 2005;112:e28-32.
677. Cannon CP, Goldhaber SZ. Cardiovascular risk stratification of pulmonary embolism. Am J Cardiol. 1996;78:1149-51.
678. Kistner RL, Sparkuhl MD. Surgery in acute and chronic venous disease. Surgery. 1979;85:31-43.
679. Juhan C, Alimi Y, Di Mauro P, Hartung O. Surgical venous thrombectomy. Cardiovasc Surg. 1999;7:586-90.
680. Plate G, Akesson H, Einarsson E, Ohlin P, Eklof B. Long-term results of venous thrombectomy combined with a temporary arterio-venous fistula. Eur J Vasc Surg. 1990;4:483-9.
681. Plate G, Einarsson E, Ohlin P, Jensen R, Qvarfordt P, Eklof B. Thrombectomy with temporary arteriovenous fistula: the treatment of choice in acute iliofemoral venous thrombosis. J Vasc Surg. 1984;1:867-76.
682. Plate G, Eklof B, Norgren L, Ohlin P, Dahlstrom JA. Venous thrombectomy for iliofemoral vein thrombosis—10-year results of a prospective randomised study. Eur J Vasc Endovasc Surg. 1997;14:367-74.
683. Sharafuddin MJ, Hicks ME. Current status of percutaneous mechanical thrombectomy.

Part III. Present and future applications. J Vasc Interv Radiol. 1998;9:209-24.
684. Kurisu Y, Kawakami K, Tada S. Improved mechanical thrombolysis with the addition of recombinant tissue-type plasminogen activator: in vitro study with use of Cr-51-labeled clots. J Vasc Interv Radiol. 1994;5:877-80.
685. Ricco JB, Dubreuil F, Reynaud P, Bordeaux J, Gamain J, Le Douarec P, et al. The LGM Vena-Tech caval filter: results of a multicenter study. Ann Vasc Surg. 1995;9 Suppl:S89-100.
686. Tai NR, Atwal A, Handa A, Platts A, Hamilton G. Vascular surgical society of great britain and ireland: caval filters are an underexploited therapy for acute pulmonary embolism. Br J Surg. 1999;86:705.
687. Decousus H, Leizorovicz A, Parent F, Page Y, Tardy B, Girard P, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. N Engl J Med. 1998;338:409-15.
688. Bovyn G, Gory P, Reynaud P, Ricco JB. The Tempofilter: a multicenter study of a new temporary caval filter implantable for up to six weeks. Ann Vasc Surg. 1997;11:520-8.
689. Zwaan M, Lorch H, Kulke C, Kagel C, Schweider G, Siemens HJ, et al. Clinical experience with temporary vena caval filters. J Vasc Interv Radiol. 1998;9:594-601.
690. Millward SF, Oliva VL, Bell SD, Valenti DA, Rasuli P, Asch M, et al. Gunther Tulip Retrievable Vena Cava Filter: results from the Registry of the Canadian Interventional Radiology Association. J Vasc Interv Radiol. 2001;12:1053-8.
691. Millward SF. Gunther Tulip retrievable filter: why, when and how? Can Assoc Radiol J. 2001;52:188-92.
692. Imberti D, Bianchi M, Farina A, Siragusa S, Silingardi M, Ageno W. Clinical experience with retrievable vena cava filters: results of a prospective observational multicenter study. J Thromb Haemost. 2005;3:1370-5.
693. Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, et al. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med. 1996;125:1-7.
694. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med. 2000;160:761-8.
695. Prandoni P. Controversial issues in the diagnosis of venous thromboembolism. Pathophysiol Haemost Thromb. 2003;33:311-3.
696. Goldhaber SZ. Prevention of recurrent idiopathic venous thromboembolism. Circulation. 2004;110:IV20-4.
697. Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med. 2001;345:165-9.
698. Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med. 2003;139:19-25.
699. Ridker PM, Goldhaber SZ, Glynn RJ. Low-intensity versus conventional-intensity warfarin for prevention of recurrent venous thromboembolism. N Engl J Med. 2003;349:2164-7.
700. Hutten BA, Prins MH, Gent M, Ginsberg J, Tijssen JG, Buller HR. Incidence of recurrent

thromboembolic and bleeding complications among patients with venous thromboembolism in relation to both malignancy and achieved international normalized ratio: a retrospective analysis. J Clin Oncol. 2000;18:3078-83.
701. Prandoni P, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood. 2002;100:3484-8.
702. Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A meta-analysis of randomized, controlled trials. Ann Intern Med. 1999;130:800-9.
703. Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. Arch Intern Med. 2000;160:181-8.
704. van Den Belt AG, Prins MH, Lensing AW, Castro AA, Clark OA, Atallah AN, et al. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev. 2000:CD001100.
705. Hettiarachchi RJ, Prins MH, Lensing AW, Buller HR. Low molecular weight heparin versus unfractionated heparin in the initial treatment of venous thromboembolism. Curr Opin Pulm Med. 1998;4:220-5.
706. Ageno W, Grimwood R, Limbiati S, Dentali F, Steidl L, Wells PS. Home-treatment of deep vein thrombosis in patients with cancer. Haematologica. 2005;90:220-4.
707. Kovacs MJ, Anderson D, Morrow B, Gray L, Touchie D, Wells PS. Outpatient treatment of pulmonary embolism with dalteparin. Thromb Haemost. 2000;83:209-11.
708. Jarrett BP, Dougherty MJ, Calligaro KD. Inferior vena cava filters in malignant disease. J Vasc Surg. 2002;36:704-7.
709. Green D, Hull RD, Brant R, Pineo GF. Lower mortality in cancer patients treated with low-molecular-weight versus standard heparin. Lancet. 1992;339:1476.
710. Siragusa S, Cosmi B, Piovella F, Hirsh J, Ginsberg JS. Low-molecular-weight heparins and unfractionated heparin in the treatment of patients with acute venous thromboembolism: results of a meta-analysis. Am J Med. 1996;100:269-77.
711. Lee AY, Rickles FR, Julian JA, Gent M, Baker RI, Bowden C, et al. Randomized comparison of low molecular weight heparin and coumarin derivatives on the survival of patients with cancer and venous thromboembolism. J Clin Oncol. 2005;23:2123-9.
712. Arepally G, Cines DB. Heparin-induced thrombocytopenia and thrombosis. Clin Rev Allergy Immunol. 1998;16:237-47.
713. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. Am J Med. 1996;101:502-7.
714. Warkentin TE, Sheppard JA, Horsewood P, Simpson PJ, Moore JC, Kelton JG. Impact of the patient population on the risk for heparin-induced thrombocytopenia. Blood. 2000;96:1703-8.
715. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126:311S-37S.
716. Girolami B, Prandoni P, Stefani PM, Tanduo C, Sabbion P, Eichler P, et al. The incidence of heparin-induced thrombocytopenia in hospitalized medical patients treated with

subcutaneous unfractionated heparin: a prospective cohort study. Blood. 2003;101: 2955-9.
717. Liu JC, Lewis BE, Steen LH, Grassman ED, Bakhos M, Blakeman B, et al. Patency of coronary artery bypass grafts in patients with heparin-induced thrombocytopenia. Am J Cardiol. 2002;89:979-81.
718. Walls JT, Curtis JJ, Silver D, Boley TM, Schmaltz RA, Nawarawong W. Heparin-induced thrombocytopenia in open heart surgical patients: sequelae of late recognition. Ann Thorac Surg. 1992;53:787-91.
719. Verma AK, Levine M, Shalansky SJ, Carter CJ, Kelton JG. Frequency of heparin-induced thrombocytopenia in critical care patients. Pharmacotherapy. 2003;23:745-53.
720. Mehta R, Golichowski A. Treatment of heparin induced thrombocytopenia and thrombosis during the first trimester of pregnancy. J Thromb Haemost. 2004;2:1665-6.
721. Wallis DE, Workman DL, Lewis BE, Steen L, Pifarre R, Moran JF. Failure of early heparin cessation as treatment for heparin-induced thrombocytopenia. Am J Med. 1999;106:629-35.
722. Kadidal VV, Mayo DJ, Horne MK. Heparin-induced thrombocytopenia (HIT) due to heparin flushes: a report of three cases. J Intern Med. 1999;246:325-9.
723. Gruel Y, Pouplard C, Nguyen P, Borg JY, Derlon A, Juhan-Vague I, et al. Biological and clinical features of low-molecular-weight heparin-induced thrombocytopenia. Br J Haematol. 2003;121:786-92.
724. Hach-Wunderle V, Kainer K, Salzmann G, Muller-Berghaus G, Potzsch B. Heparin-related thrombosis despite normal platelet counts in vascular surgery. Am J Surg. 1997;173:117-9.
725. Lubenow N, Kempf R, Eichner A, Eichler P, Carlsson LE, Greinacher A. Heparin-induced thrombocytopenia: temporal pattern of thrombocytopenia in relation to initial use or reexposure to heparin. Chest. 2002;122:37-42.
726. Rice L, Attisha WK, Drexler A, Francis JL. Delayed-onset heparin-induced thrombocytopenia. Ann Intern Med. 2002;136:210-5.
727. Greinacher A, Amiral J, Dummel V, Vissac A, Kiefel V, Mueller-Eckhardt C. Laboratory diagnosis of heparin-associated thrombocytopenia and comparison of platelet aggregation test, heparin-induced platelet activation test, and platelet factor 4/heparin enzyme-linked immunosorbent assay. Transfusion. 1994;34:381-5.
728. Greinacher A, Potzsch B, Amiral J, Dummel V, Eichner A, Mueller-Eckhardt C. Heparin-associated thrombocytopenia: isolation of the antibody and characterization of a multimolecular PF4-heparin complex as the major antigen. Thromb Haemost. 1994;71:247-51.
729. Newman PM, Chong BH. Heparin-induced thrombocytopenia: new evidence for the dynamic binding of purified anti-PF4-heparin antibodies to platelets and the resultant platelet activation. Blood. 2000;96:182-7.
730. Kelton JG, Sheridan D, Santos A, Smith J, Steeves K, Smith C, et al. Heparin-induced thrombocytopenia: laboratory studies. Blood. 1988;72:925-30.
731. Warkentin TE, Hayward CP, Boshkov LK, Santos AV, Sheppard JA, Bode AP, et al. Sera from patients with heparin-induced thrombocytopenia generate platelet-derived microparticles with procoagulant activity: an explanation for the thrombotic complications of heparin-induced thrombocytopenia. Blood. 1994;84:3691-9.
732. Amiral J, Wolf M, Fischer A, Boyer-Neumann C, Vissac A, Meyer D. Pathogenicity of

IgA and/or IgM antibodies to heparin-PF4 complexes in patients with heparin-induced thrombocytopenia. Br J Haematol. 1996;92:954-9.
733. Walenga JM, Jeske WP, Prechel MM, Bakhos M. Newer insights on the mechanism of heparin-induced thrombocytopenia. Semin Thromb Hemost. 2004;30 Suppl 1:57-67.
734. Fareed J, Walenga JM, Hoppensteadt DA, Jeske WP, Lietz H, Ahmad S, et al. Selectins in the HIT syndrome: pathophysiologic role and therapeutic modulation. Semin Thromb Hemost. 1999;25 Suppl 1:37-42.
735. Pouplard C, Iochmann S, Renard B, Herault O, Colombat P, Amiral J, et al. Induction of monocyte tissue factor expression by antibodies to heparin-platelet factor 4 complexes developed in heparin-induced thrombocytopenia. Blood. 2001;97:3300-2.
736. Visentin GP, Ford SE, Scott JP, Aster RH. Antibodies from patients with heparin-induced thrombocytopenia/thrombosis are specific for platelet factor 4 complexed with heparin or bound to endothelial cells. J Clin Invest. 1994;93:81-8.
737. Blank M, Shoenfeld Y, Tavor S, Praprotnik S, Boffa MC, Weksler B, et al. Anti-platelet factor 4/heparin antibodies from patients with heparin-induced thrombocytopenia provoke direct activation of microvascular endothelial cells. Int Immunol. 2002;14:121-9.
738. Sheridan D, Carter C, Kelton JG. A diagnostic test for heparin-induced thrombocytopenia. Blood. 1986;67:27-30.
739. Chong BH, Burgess J, Ismail F. The clinical usefulness of the platelet aggregation test for the diagnosis of heparin-induced thrombocytopenia. Thromb Haemost. 1993;69:344-50.
740. Walenga JM, Jeske WP, Fasanella AR, Wood JJ, Bakhos M. Laboratory tests for the diagnosis of heparin-induced thrombocytopenia. Semin Thromb Hemost. 1999;25 Suppl 1:43-9.
741. Walenga JM, Jeske WP, Fasanella AR, Wood JJ, Ahmad S, Bakhos M. Laboratory diagnosis of heparin-induced thrombocytopenia. Clin Appl Thromb Hemost. 1999;5 Suppl 1:S21-7.
742. Pouplard C, Amiral J, Borg JY, Laporte-Simitsidis S, Delahousse B, Gruel Y. Decision analysis for use of platelet aggregation test, carbon 14-serotonin release assay, and heparin-platelet factor 4 enzyme-linked immunosorbent assay for diagnosis of heparin-induced thrombocytopenia. Am J Clin Pathol. 1999;111:700-6.
743. Lindhoff-Last E, Eichler P, Stein M, Plagemann J, Gerdsen F, Wagner R, et al. A prospective study on the incidence and clinical relevance of heparin-induced antibodies in patients after vascular surgery. Thromb Res. 2000;97:387-93.
744. Ahmad S, Haas S, Hoppensteadt DA, Lietz H, Reid U, Bender N, et al. Differential effects of clivarin and heparin in patients undergoing hip and knee surgery for the generation of anti-heparin-platelet factor 4 antibodies. Thromb Res. 2002;108:49-55.
745. Lewis BE, Wallis DE, Leya F, Hursting MJ, Kelton JG. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Arch Intern Med. 2003;163:1849-56.
746. Lewis BE, Wallis DE, Berkowitz SD, Matthai WH, Fareed J, Walenga JM, et al. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation. 2001;103:1838-43.
747. Greinacher A, Lubenow N, Eichler P. Anaphylactic and anaphylactoid reactions associated with lepirudin in patients with heparin-induced thrombocytopenia. Circulation. 2003;108:2062-5.
748. Eichler P, Friesen HJ, Lubenow N, Jaeger B, Greinacher A. Antihirudin antibodies in patients with heparin-induced thrombocytopenia treated with lepirudin: incidence, effects

on aPTT, and clinical relevance. Blood. 2000;96:2373-8.
749. Magnani HN. Heparin-induced thrombocytopenia (HIT): an overview of 230 patients treated with orgaran (Org 10172). Thromb Haemost. 1993;70:554-61.
750. Chong BH, Gallus AS, Cade JF, Magnani H, Manoharan A, Oldmeadow M, et al. Prospective randomised open-label comparison of danaparoid with dextran 70 in the treatment of heparin-induced thrombocytopaenia with thrombosis: a clinical outcome study. Thromb Haemost. 2001;86:1170-5.
751. Farner B, Eichler P, Kroll H, Greinacher A. A comparison of danaparoid and lepirudin in heparin-induced thrombocytopenia. Thromb Haemost. 2001;85:950-7.
752. Kodityal S, Manhas AH, Udden M, Rice L. Danaparoid for heparin-induced thrombocytopenia: an analysis of treatment failures. Eur J Haematol. 2003;71:109-13.
753. Haas S, Walenga JM, Jeske WP, Fareed J. Heparin-induced thrombocytopenia: clinical considerations of alternative anticoagulation with various glycosaminoglycans and thrombin inhibitors. Clin Appl Thromb Hemost. 1999;5:52-9.
754. Tardy B, Tardy-Poncet B, Viallon A, Piot M, Mazet E. Fatal danaparoid-sodium induced thrombocytopenia and arterial thromboses. Thromb Haemost. 1998;80:530.
755. Greinacher A, Alban S, Dummel V, Franz G, Mueller-Eckhardt C. Characterization of the structural requirements for a carbohydrate based anticoagulant with a reduced risk of inducing the immunological type of heparin-associated thrombocytopenia. Thromb Haemost. 1995;74:886-92.
756. Walenga JM, Koza MJ, Lewis BE, Pifarre R. Relative heparin-induced thrombocytopenic potential of low molecular weight heparins and new antithrombotic agents. Clin Appl Thromb Hemost. 1996:S21-7.
757. Elalamy I, Lecrubier C, Horellou MH, Conard J, Samama MM. Heparin-induced thrombocytopenia: laboratory diagnosis and management. Ann Med. 2000;32 Suppl 1:60-7.
758. Fohlen-Walter A, De Maistre E, Mulot A, Marchand-Arvier M, Lecompte T. Does negative heparin-platelet factor 4 enzyme-linked immunosorbent assay effectively exclude heparin-induced thrombocytopenia? J Thromb Haemost. 2003;1:1844-5.
759. Messmore H, Jeske W, Wehrmacher W, Walenga J. Benefit-risk assessment of treatments for heparin-induced thrombocytopenia. Drug Saf. 2003;26:625-41.
760. Hirsh J, Heddle N, Kelton JG. Treatment of heparin-induced thrombocytopenia: a critical review. Arch Intern Med. 2004;164:361-9.
761. Warkentin TE, Elavathil LJ, Hayward CP, Johnston MA, Russett JI, Kelton JG. The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. Ann Intern Med. 1997;127:804-12.
762. Srinivasan AF, Rice L, Bartholomew JR, Rangaswamy C, La Perna L, Thompson JE, et al. Warfarin-induced skin necrosis and venous limb gangrene in the setting of heparin-induced thrombocytopenia. Arch Intern Med. 2004;164:66-70.

Printed in Cyprus by Chr. Nicolaou & Sons Ltd